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ARTÍCULO ORIGINAL

Current status of heparinization and monitoring of anticoagulation during extracorporeal circulation in adult patients: trends in Latin America.

Estado actual de la heparinización y monitoreo de la anticoagulación durante circulación extracorpórea en pacientes adultos: tendencias en latinoamérica.

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RESUMEN

Introduction: The development of cardiac surgery with extracorporeal circulation would not have been possible without the discovery of heparin. This is the anticoagulant of choice for the initiation and maintenance of extracorporeal circulation due to its efficacy and easy reversal. However, several factors cause the anticoagulant effect to be different between patients.

Objectives: To determine trends and discrepancies in the management and monitoring of heparinization used by Latin American perfusionists in adult patients undergoing cardiac surgery with extracorporeal circulation.

Methods: A prospective descriptive study was carried out by applying a 13-question survey. Data were expressed in percentages and confidence intervals. trend considering the answers that exceeded 51% and the rest were valued as discrepancies.

Results: Of the 269 respondents, it was found that: 54.1% administered 300 IU/kg of systemic heparin. 66.2% add 5 000 IU of heparin to the prime. 68.1% use the same dose of heparin in obese patients. 57.1% add 5 000 to 10 000 IU of heparin when the ACT does not reach a safe threshold. 99.6% administered bolus heparin. If heparin resistance is suspected, 82.7% administer fresh frozen plasma. 53.2% reversed heparin in a 1:1 ratio with protamine.

Conclusion: In Latin America, there are varied heparinization and anticoagulation monitoring strategies, showing a more homogeneous trend in terms of heparinization strategies compared to anticoagulation monitoring during ECC.

Keywords: **Extracorporeal Circulation, Anticoagulation, Activated Coagulation Time, Heparin,**

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SUMMARY

Introducción: El desarrollo de la cirugía cardiaca con circulación extracorpórea no hubiera sido posible sin el descubrimiento de la heparina, el anticoagulante de elección para el inicio y mantenimiento de la circulación extracorpórea, por su eficacia y fácil reversión. Sin embargo, una cantidad de factores hacen que el efecto anticoagulante sea diferente entre los pacientes.

Objetivos: Determinar las tendencias y discrepancias en el manejo y monitoreo de la heparinización utilizadas por los perfusionistas latinoamericanos en pacientes adultos sometidos a cirugía cardiaca con CEC.

Métodos: Se realizó un estudio descriptivo prospectivo mediante la aplicación de una encuesta de 13 preguntas. Los datos fueron expresados en porcentajes e intervalos de confianza. Se consideró tendencia las respuestas que superaron el 51% y las respuestas restantes discrepancia.

Resultados: De los 269 encuestados se encontró que: el 54,1% administra 300 UI/kg de heparina sistémica. El 66,2% agrega 5 000 UI de heparina al cebado. El 68,1% utiliza la misma dosis de heparina en pacientes obesos. El 57,1% agrega de 5 000 a 10 000 UI de heparina cuando el TCA no alcanza un umbral seguro. El 99,6% administra la heparina por bolos. Si se sospecha resistencia a la heparina el 82,7% administra plasma fresco congelado. El 53,2% revierte la heparina en relación 1:1 con la protamina.

Conclusión: En Latinoamérica existen estrategias variadas de heparinización y monitorización de la anticoagulación, se evidenció una tendencia más homogénea en cuanto a las estrategias de heparinización respecto a la monitorización de la anticoagulación durante la CEC.

Palabras clave: **Circulación Extracorpórea, Anticoagulación, Tiempo de Coagulación Activado, Heparina, Perfusión en Latinoaméica, ALAP**

INTRODUCTION

Extracorporeal Circulation (ECC), one of the greatest breakthroughs in the field of heart surgery, is not free from difficulties and challenges. Contact of blood with the circuit, blood aspiration from the surgical field to the venous reservoir, physical damage to blood components, linear flow, hemodilution, hypothermia and many other ECC-associated blood physiology alterations can induce leukocyte activation, release of inflammation mediators, formation of free radicals, activation of complement system, kallikrein release, platelet activation, and stimulation of the coagulation fibrinolytic cascade. Therefore, one of the most important factors for the success of ECC is to achieve adequate anticoagulation.[1]

Heparin was discovered back in 1916 by McLean, who isolated a fat-soluble anticoagulant of canine liver tissue. In 1918, Howell called it heparin, from the Greek word for liver, "hepar." The first heparin product was manufactured and released for IV use by the Swedish company Vitrum AB in 1936. It has been used since the first surgery performed by Dr. Gibbon. It is currently used thanks, among other factors, to a) its low economic cost, rapid action, short half-life, efficacy, easy analytical control, and the availability of an immediate reversion agent. All this is probably responsible for its widespread use worldwide.[2-4]

Traditional unfractionated heparin (UFH) is a heterogeneous mixture of 5 to 35 polysaccharides with sequences that contain glucosamine and sulfated glucuronic or iduronic acid whose molecular weights range between 5 000 and 30 000 Da (mean, 15 000 Da). It is a natural compound isolated from bovine or porcine bowels. Its main mechanism of action is mediated indirectly by catalyzing the anticoagulant effect of antithrombin (AT), inactivating coagulant factors IXa, Xa, Xia, and XIIa, and thrombin (factor IIa), thereby preventing conversion of fibrinogen to fibrin. By inhibiting the activation of factor XIII, it also prevents stable fibrin clots from forming. The length of heparin chain should contain a minimum of 18 saccharides to form a ternary complex of heparin/AT/thrombin and act as a

template on which both AT and thrombin can interact. When this complex is formed, inhibition of thrombin in its liquid phase accelerates 4000 times. Alternatively, the inhibition of Xa factor by AT can occur in chains of smaller lengths and it only requires heparin to have the ideal pentasaccharides sequence. Acceleration of factor X inhibition is 1200 times.[5]

Heparin pharmacokinetics is complex and variable even before considering the effects of hemodilution, hypothermia, ECC, and organ dysfunction during heart surgery. After IV administration, heparin immediately binds to several plasma proteins, macrophages, and endothelial cells. Heparin purge is performed in two phases. Rapid saturation phase consists of heparin internalization and metabolism both in endothelial cells and macrophages. The subsequent clearing is slower, and largely occurs through renal clearance. Due to this pharmacokinetic profile, the highest dosage results in an increased intensity and duration of anticoagulant effect. The biological half-life of heparin increases from 30 minutes, with an IV bolus of 25 IU/kg up to 60 minutes with an IV bolus of 100 IU/kg and up to 150 minutes with an IV bolus of 400 IU/kg. The clearance half-life of low molecular weight heparin is 3 to 6 hours.[6]

Activated Clotting Time (ACT) developed by Hattersley in 1966 and Partial Thromboplastin Time (PTT) was developed by Blakely in 1968 marked the beginning of research in the field of anticoagulation in ECC. In 1975, Bull and his team detected the wide variability of heparin response to the different heparin dosage protocols, and proposed the following: baseline ACT, early bolus of 200 IU/kg and new ACT at 5 minutes. From these data it is possible to obtain an individual dosage-response curve with the amount of heparin in the X axis and the results of ACT in the Y axis. This allows us to extrapolate successive ACT values, estimate the patient's heparin needs, and determine protamine to revert it. In addition, they recommended an ACT value of around 480 s.[7]

Since Bull's study to the present ACT has been the standard to monitor anticoagulation during ECC by virtue of its simplicity, safety, cost, and relative effectiveness. However, during ECC, ACT can extend significantly due to hemodilution and hypothermia. Studies have also found that the level of ACT does not accurately reflect plasma levels of circulating heparin compared to sensitive trials for heparin concentration in plasma.[7]

The effect of heparin can vary, depending on the amount of AT, the bind of plasma, proteins macrophages, and fixation to endothelial cells. Other aspects like blood volume, septic states, certain coagulation associated disorders, the administration of certain drugs like acenocoumarol, or antiplatelet therapy, age, sex, body surface, temperature, and even the drug brand can influence, in turn, heparin response. Therefore, we cannot establish a linear relation among the heparin administered, the level of circulating heparin and the degree of anticoagulation obtained. In addition, ECC contributes characteristics that can also alter this response such as hemodilution, hypothermia, and biocompatible coatings.[2,8]

Achieving proper anticoagulation is a challenge when response to systemic heparin is not what we expect. Although Antithrombin deficiency can be the lead cause of heparin resistance, the mechanism is complex and multifactorial.1 In these cases, the following formula allows us to calculate the heparin sensitivity index (HSI).

Values < 1.3 were considered indicators of heparin resistance.8 Also, there are different models and brands of machines used to run this test, the results obtained with devices from different manufacturers are also different, and centers can change from one to the next based on their practice depending on their own experience with a certain device. ACT reflects the overall status of a patient's hemostasis, therefore, the ACT and anti-Xa activity do not correlate well in ECC.[8,9]

A small study conducted at Hospital Barts Health NHS Trust London, United Kingdom, reported that after running tests on all their ACT machines to guarantee an acceptable degree of precision among instruments, samples were collected from 31 patients at the beginning and 3 minutes after the administration of a bolus of heparin. ACT was measured in the OR while a different sample (from the same blood drawn),was sent to the laboratory to measure anti-Xa activity. They found no correlation between ACT and anti-Xa activity despite acceptable ACT values in ECC. This was surprising since this sample was collected before ECC and, therefore, should not have been bound to the usual confounding factors of hemodilution and hypothermia.[9]

Events associated with the production of heparin should be considered: in 1990, the so-called "mad cow disease" caused the

replacement of heparin from bovine to porcine origin, which brought about a change in anticoagulant activity. In 2007 and 2008 there was an international crisis when the production of porcine heparin from China became contaminated, and reintroduction of bovine heparin was considered. As a result, since 2009, the Food and Drug Administration (FDA) has been recommending the use of bovine intestine as a source while making adjustments in heparin dosage taking into account a reduction in the drug function in approximately 10% of the cases.[12] The dosage used varies from 300 to 400 IU/kg to achieve ACT > 480 s. However, there is no consensus in the medical literature regarding what dose of heparin is safer and more effective during ECC both in the induction (systemic dose) and circuit prime, and subsequent doses to keep ideal anticoagulation in terms of minimizing thromboembolic and hemorrhagic complications. There are patients who require early doses higher compared to those described to inactivate thrombin to a sufficient degree. An example of this is patients who have received IV heparin infusions prior to the procedure, in whom an initial dose of 400 IU/kg is routinely administered.[3,8]

In a study on patients undergoing heart surgery with ECC, the safety and efficacy profile of heparin was compared in two groups, one of them was administered 200 IU/kg and the other one 300 IU/kg. Results were compared regarding postoperative bleeding, need for transfusions, postoperative differences in platelet count, etc. The authors concluded that use of a dose of heparin > 300 IU/kg compared to a dose < 200 IU/kg does not contribute any benefits regarding better protection of coagulation system, isn't associated with any differences in postoperative bleeding or with use of blood products, etc.[3]

A survey conducted among 2972 members of the American Society of Cardiovascular Anesthesiologists revealed 550 answers analyzed based on the following results: 74.9% of the respondents used an empirical approach based on weight to determine heparin bolus prior to ECC. The doses used were 300-400 IU/kg. The maximum dose of heparin that respondents administered before initiating additional therapy to achieve a target activated clotting time was as high as 660 IU/kg. Most respondents also added heparin to the ECC circuit. An ACT value of 400 to 480 s was used in 70.7% of the patients. Regarding heparin resistance, around half of respondents felt that it occurred in 1% to 10% of the ECC cases performed. Antithrombin concentrate was administered in 54.2% of the cases compared to fresh frozen plasma as first-line therapy.[11]

The objective of a different study was to compare the impact on variability in the anticoagulation of continuous administration of heparin vs administration in boluses using ACT values during ECC. The administration of heparin during ECC was conducted in two ways; one with the standard technique where it is added on demand (bolus) and another one through the continuous perfusion through a pump (infusion). As a result, it was revealed that the administration of heparin during ECC, with continuous infusion, facilitates better anticoagulation control. Therefore, there was less variability in ACT determinations and more values remained within optimal ranges significantly.2

After reviewing the medical literature available, we observed that there is no standardization regarding the doses of heparine used during ECC in heart surgery; in addition, there are few studies on this topic in Latin America and across the world. Therefore, this question pops us: How is the management and monitoring of heparinization used by Latin-American perfusionists for adult patients undergoing surgical procedures with extracorporeal circulation?

ENDPOINTS

General Endpoint

To know the current condition of the managing and monitoring of heparinization used by Latin-American perfusionists for adult patients undergoing surgical procedures with extracorporeal circulation and evaluate Latin-American trends.

Specific endpoints:

1. To identify the dose of systemic heparin and in the prime prior to the use of ECC in adult patients that undergo heart surgery in Latin America.

2. To know the Activated Clotting Time range considered by perfusionists as optimal for using ECC in adult patients that undergo heart surgery in Latin America.

3. To determine the interventions performed by Latin-American perfusionists when the Activated Clotting Time value is below the optimal level expected in the different possible scenarios during ECC in adult patients that undergo heart surgery.

4. To know the techniques of heparin administration used during ECC in adult patients treated with heart surgery in Latin America.

5. To identify the strategies used for the heparinization of obese patients who undergo surgery with ECC in Latin America.

6. To stage by Latin-American region the scope and response capabilities of the perfusionist population based on their availability to provide information through this data collection method.

METHOD

A descriptive prospective study was conducted by applying a survey made up of 12 questions to know the anticoagulation strategies used by Latin-American perfusionists in their everyday work in view of the different situations (Annex 1). The survey was later validated by the Latin-American Perfusion Association (ALAP).

After the questions were validated, and the survey was created on the QuestionPro platform https://www.questionpro.com the next step was to send this link through different social media to the different perfusionist associations in the different Latin-American countries. The survey remained open for up to three weeks (from January through February 2022).

To define the minimum safe anticoagulation cut-off values during ECC, we took the reference values described in the guidelines on the management of the patient's blood regarding adult heart surgery, where a Class IIa Recommendation with Evidence Level C is considered for an ACT of 480 s. It was also identified that there can be variations of these values depending on the circumstances like, for instance, hemodilution, hypothermia, and the machine used for determining this value. Therefore, a Class IIa Recommendation with Evidence Level C was identified for ACT values of 400 s as the lowest ACT limit to maintain "ECC without coagulation."[13]

The data obtained from all the surveys that were fully answered without omitting any answers were included. The study excluded the survey questions answered by perfusionists who were not members of Latin-American countries, and those that were received incomplete or with more than one option marked for each answer.

The tool to obtain the answers was sent to an estimate 700 perfusionists from the Latin-American Perfusion Association. To distribute the surveys, the emails registered in the ALAP database were used. In addition, the digital link to the survey was circulated through the different social media.

No incentives of any kind were offered to the perfusionists who participated in the survey sent.

Statistical processing:

To determine the sample size, the confidence interval (CI) of 95% was calculated as well as a 0.5 proportion of the sample. Therefore, it was revealed that it would take 249 respondents to reach a 5% overall margin of error. Descriptive statistics was used. To this end, data were recodified in dichotomic variables. Results were expressed in percentages and frequency tables were built with proportions and bar charts to summarize the data and make them easier to understand. CI was used for proportions established in 95%. Those data obtained with proportionS ≥ 51% and discrepancies ≤ 50% were considered a trend. All the calculations were made using the statistical software package SPSS version 2.5 (IBM Corp 64 Bits version).

RESULTS AND DISCUSSION

During the time that the survey remained available, a total of 271answers were collected. The response rate was 40% (271 out of 700) (Figure 1). As shown in the following diagram, two different surveys were identified and excluded; one survey answered in Spain and another one received with blank answers so they were both eliminated from out database. On the other

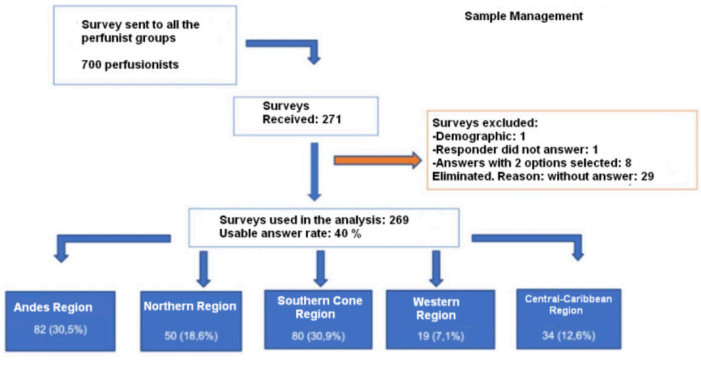

Figure 1. Diagram describing the distribution of the answers received and the reasons why certain answers were not considered in the final analysis.

hand, 8 surveys were identified as having answers that had checked two or more options (instead of one). Therefore, these double answers were not considered for the data analysis either.

Therefore, we obtained a total of 269 valid answers. The existence of a trend or discrepancy in the heparinization strategies in Latin America was considered by consensus among the authors. In addition, it was agreed that the data obtained with proportions or percentages ≥ 51% would be called a trend and discrepancies would be considered as such if ≤ 50%.

The answers came from Latin-American perfusionists distributed in the 5 regions established for the Latin-American Perfusion Association. Out of the total number of surveys answered by Latin-American perfusionists, the Southern Cone Region had the highest percentage of participants with 30.9% followed by the Andes with 30.5%, the Northern Region (18.6%), the Central Caribbean Region (12.6%), and finally the Southwestern Region (7.1%). (Table 1).

Although the Andes region had the highest percentage of participation, we should mention that the countries with the largest number of respondents were, in this order, Mexico, Argentina, Colombia, Chile, and Peru. Although Brazil has a large number of perfusionists, they did not welcome the survey very warmly due to the language barrier. The choice of questions was done considering two great topics of discussion like heparin management and anticoagulation monitoring during surgical procedures with ECC in Latin America. As far as the authors know, this was the first Latin-American survey of this kind, and the results can be compared to some recommendations issued by the latest international STS/ SCA/AmSECT and EACTS/ EACTA/EBCP clinical guidelines.

According to the results obtained, Latin-American perfusionists have different ways of managing and monitoring anticoagulation of patients treated with ECC both in terms of the heparin doses administered to the patient and the circuit and the ACT values managed during the procedures as can be observed in the summary shown on table 2.

Regarding the dose of systemic heparin of the perfusionists surveyed 54.1% (48.1-60.1) use 300 IU/kg while 36.6% (CI, 30.7-42.3) use 400 IU/kg, 5.2% (CI, 2.5-7.9) refer that they use 200 IU/kg and 5.2% (CI, 2.5 – 7.9) use doses different to these (Graph 1). The STS/SCA/AmSECT clinical practice guidelines

Table 1. Demographic data of Latin-American perfusionists who participated in the survey

ALAP Region	**n (%)**
The Andes Region	82 (30.48)
Venezuela	14 (5.20)
Colombia	29 (10.78)
Peru	25 (9.29)
Ecuador	10 (3.71)
Bolivia	4 (1.48)
Northern Region	**50 (18.58)**
Mexico	50 (18.58)
Southern cone Region	83 (30.85)
Argentina	38 (14.12)
Uruguay	12 (4.46)
Paraguay	4 (1.48)
Chile	29 (10.78)
South-western Region	**19 (7.06)**
Brazil	19 (7.06)
Central Caribbean Region	34 (12.63)
Guatemala	3 (1.11)
Honduras	1 (0.37)
El Salvador	1 (0.37)
Nicaragua	1 (0.37)
Costa Rica	5 (1.85)
Panamá	6 (2.23)
Dominican Republic	7 (2.60)
Cuba	3 (1.11)
Puerto Rico	4 (1.48)
Jamaica	2 (0.74)

Table 2. Results of the survey "Strategies in the management of heparinization and monitoring of anticoagulation in adult patients undergoing extracorporeal circulation: Tendencies in Latin America

Heparin Management	n (%)	95% IC
Systemic heparin dosage before starting ECC.		
200 UI/kg	11 (4,1)	1,7 - 6,5
300 UI/kg	144 (54,1)	48,1 - 60,1
400 UI/kg	98 (36,6)	30,7 - 42,3
Other	14 (5,2)	2,5 - 7,9
Heparin dosage used to prime the ECC circuit.		
5 000 UI	174 (66,2)	60,4 - 71,9
10 000 UI	60 (22,8)	17,7 -22,8
15 000 UI	6 (2,3)	0,4 - 4,1
100 U/kg	23 (8,7)	5,3 - 12,1
Method of heparin administration used during ECC.		
Bolus	261 (99,6)	100 - 101
Continuous Infusion	1 (0,4)	-0,3 - 1,3
Systemic heparin dosage in obese patients.		
Same formula for all the patients	184 (68,1)	62,5 - 73,4
BMI estimate	21 (7,8)	4,5 - 10,9
Lean weight estimate	44 (16,3)	11,8 - 20,7
Patient's characteristics/circulatory arrest	21 (7,8)	4,5 - 10,9
Number of heparin brands.		
1	128 (48,3)	42,2 - 54,3
2	99 (37,4)	31,5 - 43,2
3	24 (9,1)	5,8 - 12,5
More than 3	14 (5,3)	2,5 - 7,9
Heparin - protamine ratio.		
0.8 : 1.0	55 (20,6)	17,8 - 28,0
1.0 : 1.0	141 (53,2)	45,0 - 57,0
1.0 : 1.2	36 (13,6)	9,4 - 17,6
1.0 : 1.5	33 (12,5)	8,4 - 16,3

Monitoring anticoagulation	n (%)	95% IC
ACT range considered optimal to start ECC.		
380 - 420 seg	51 (18,9)	14,1 - 23,5
420 - 460 seg	52 (19,3)	14,5 - 23,9
460 - 500 seg	136 (50,4)	44,3 - 56,3
Over 500 sec	31 (11,5)	7,6 - 15,3
Heparin dosage administered to the ECC circuit if ACT is below optimal level.		
2 500 UI	37 (13,9)	9,7 -18,1
5 000 - 10 000 UI	152 (57,1)	50,9 - 62,9
10 000 - 15 000 UI	3 (1,1)	0,1 - 2,4
100 U/kg	73 (27,4)	22,1 - 32,9
Do not administer	1 (0,4)	- 0,3 - 1,1
Heparin dose administered to the ECC circuit if ACT is below optimal level and is about to finish		
la CEC.	78 (29,1)	23,6 - 34,5
2 500 UI	48 (17,9)	13,2 - 22,5
5 000 - 10 000 UI	0	
10 000 - 15 000 UI	20 (7,5)	4,3 - 10,6
100 U/kg	122 (45,5)	39,5 - 51,5
Do not administer		
ACT measuring system.		
ACT Plus	122 (45,4)	39,3 -51,3
Hemochron	90 (33,5)	27,7 - 39,1
Hemochron Jr	18 (6,7)	3,6 - 9,7
Istad	15 (5,6)	2,8 - 8,3
Other	24 (8,9)	5,4 - 12,3
Methods used to reach adequate ACT levels if heparin resistance is suspected.		
Fresh frozen plasma	220 (82,7)	78,1 - 87,2
Antithrombin III	13 (4,9)	2,2 - 7,4
Albumin	12 (4,5)	2,0 - 7,0
Hirudin	3 (1,1)	-0,1 - 2,4
Other	18 (6,8)	3,7 - 9,8
Time elapsed between systemic heparinization and ACT		
3 min	135 (50)	42,2 - 57,4
5 min	93 (34,4)	28,5 - 40,0
7 min	5 (1,9)	0,0 - 2,9
10 min	34 (12,6)	8,7 - 16,8
Other	3 (1,1)	- 0,3 - 1,1

on anticoagulation acknowledge the use of heparin depending on the patient's weight as a Class IIa recommendation, Evidence Level C. However, it also acknowledges that there is no clear consensus on the exact calculation of this early dose due to the heterogeneity of heparin formulations and each patient's variable response.

The pharmacodynamics of heparin depends, to a large extent, on the level and function of ATIII in plasma, patients with preoperative hypercoagulability or reduced ATIII response capacity may need to increase circulating heparin levels to attain ACT therapeutic value before ECC. There is no consensus in the current medical literature on the safest, most effective dose of heparin in terms of adequate anticoagulation and less bleeding. In his study of 1093 patients, Parada compares two anticoagulation protocols with doses of 200 IU/kg and 300 IU/kg without finding that one dosage in particular is better than the other regarding better protection of the coagulation system or in relation to the amount of postoperative bleeding.[3]

The 2017 EACTS/EACTA guidelines on the management of patient blood for adult heart surgery acknowledges that it is generally dosed based on the patient's body weight between 300 and 600 IU of systemic heparin. However, this strategy has limitations such as heparin resistance, which can lead to insufficient anticoagulation and the postoperative rebound

effect that contributes to postoperative bleeding. Instead, we should mention individualized heparin management with the use of devices that perform heparin titration based on a dose-response test such as HMS/HepCon (Medtronic, Minneapolis, MN, United States.), Hemochron RxDx (Accriva Diagnostics, San Diego, CA, United States) or anti-Xa, in addition to ACT. However, randomized, controlled studies are lacking to better assess its benefits.[13] On the other hand, in 2009, the FDA published on its website a statement addressed to healthcare professionals reporting 10% less anticoagulant activity in the new heparin compared to heparin manufactured before 2009. Still, more than half of the population studied maintains systemic doses of 300 IU/kg to start extracorporeal circulation.[3,12]

Similarly to anticoagulation, the STS/SCA/AmSECT clinical practice guidelines indicate that an anticoagulation test should be performed through a functional analysis via standardized whole-blood simulation that should confirm that anticoagulation is adequate before the start and at regular intervals during ECC.[13] There are different trends in Latin America regarding the waiting time to conduct the follow-up ACT after the patient's systemic heparinization (Chart 2), and since the anticoagulant effect of unfractionated heparin is immediate, half of the respondents (50%) (CI, 42.2 – 57.4) take the ACT sample 3 minutes after administering heparin, which is consistent with most references reported for anticoagulation management in ECC. However, 34.4% (CI, 28.5 – 40.0) do so 5 minutes later. Therefore, there is an increase in the result of ACT although has not been confirmed scientifically, the remaining 19% waits 7 or more minutes to take the sample and verify ACT.

Another question posed by our study had to do with knowing the ACT values considered optimal by perfusionists in Latin America for starting ECC. The history of establishing a safe cut-off value dates back to 1975, when Bull et al. demonstrated that with ACT > 300 s no clots formed in the reservoir or the circuit.[14]

Shortly after, Young et al. demonstrated the formation of fibrin in an animal model (primates), using this cut-off value (300 s). The study first recommended increasing this value to 400 s when it was demonstrated that it was safe in a five-patient series and additionally increasing it up to 480 s as a reasonable safety margin.[15] That is how the 480 s cut-off value was defined as the safe minimum for use during ECC, but with a limited evidence level. In our study, 50.4% (CI, 44.3 – 56.3) of the

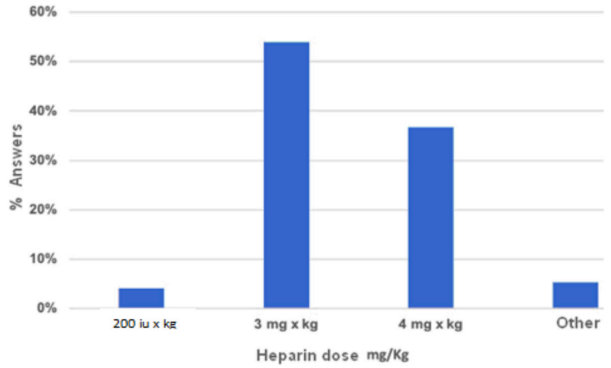

Chart 1. Dose of systemic heparin used in Latin America.

respondents considered ACT between 460 – 500 s as an optimal cut-off value (Chart 3.), which is consistent with the theoretical range described before, which in turn we found everywhere in the scientific literature available on this topic. In addition, it is a recommendation with Evidence Level C according to the anticoagulation guidelines during ECC according to the Thoracic Surgery Society, The Cardiovascular Anesthesiologist Society, and the American Society of Extracorporeal Technology.[16]

The use of significantly higher values (480 s) can be interesting if we keep in mind that there is a trend to overestimate heparin concentration when in vitro ACT is used as the only method to evaluate anticoagulation. This is a common practice in our region as described below in this study. This phenomenon is due, among other factors, to the use of different machines to determine ACT, hypothermia, low hemoglobin concentration, and the use of pharmacological agents.[17] In the survey conducted 11.5% (CI, 7.6 – 15.3) considered that ACT > 500 s was a safe cut-off value. On the other hand, 19.3% (CI, 14.5 – 23.9) use ranges between 420 s and 460s while 18.9% (CI, 14.1 – 23.5) consider 380 – 420 s as the optimal ACT to start ECC. The use

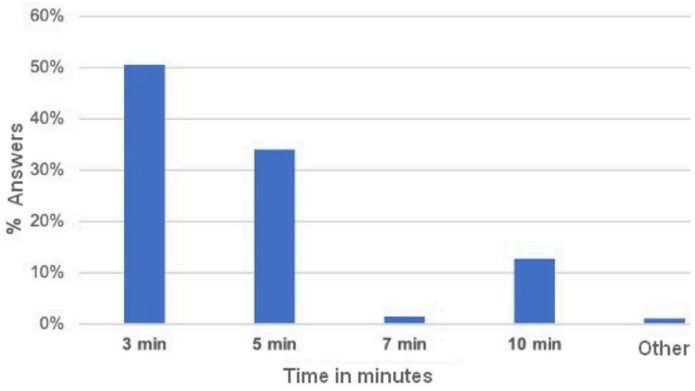

Chart 2. Time elapsed between systemic heparinization and ACT.

of ACT values < 480 s has also been described widely in the medical literature available especially associated with the use of heparin-coated circuits and mini-circuits.

In a study published by Cardoso et al., it is concluded that, compared to standard ACT of 450 s, reduction to values between 250 s and 300 s did not cause any significant increases in coagulation parameters after 3 h on ECC.[18] However, a different study published by Mirrow et al. that compared the use of conventional heparinization vs the use of low-range heparinization during the use of conventional circuits and heparin-coated circuits, found an increased production of thrombin after 60 min on ECC in the group that handled low ACT values but > 240 s and coated circuits compared to the group of circuits coated with total heparinization (ACT > 450 s). On the other hand, they found non-significant evidence of less bleeding in the group with reduced heparinization.[19]

Regarding the dose of heparin used for priming the extracorporeal circuit prior to the use of ECC, 66.2% of the respondents add 5000 IU, 22.8% add 10 000 IU, 2.3% add 15 000 IU, and 8.7% add 100 IU/kg. (Chart 4). In the last survey sent to adult heart surgery anesthesiologists ("Practices for priming anticoagulation pumps in heart surgery: results of the worldwide survey on cardiac shunt") it has been reported that heparin was the main additive used with the highest frequency for priming all across the world (43.0%). Also, there were great variations regarding regional practices. Therefore, it was among respondents from Australia and New Zealand that the highest rate of heparin use for priming was seen (65.7%) while it is reduced significantly in South America (16.3%). However, this percentage may be higher due to the relatively low response rate in South America. Regarding the medical literature available, in his book "Physiology and extracorporeal circulation techniques" Gomar indicates that 100 IU/kg can be administered for priming. In his study "Basics of cardiopulmonary bypass" Sarkar, M suggests 3 to 4 IU of heparin per mL of priming while in his book "Cardiopulmonary bypass and mechanical support: principles and practice" Gravlee recommends 1 000 to 2500 IU per liter of priming liquid for the ECC circuit.[20,21] In other studies on anticoagulation reviewed the use of heparin for priming goes from 2000 to 10 000 IU.2,3 This variability can also be noted among Latin-American perfusionists.

Upon consulting the respondents about the method of heparin administration used during ECC, when ACT does not reach the safety threshold, it was revealed that 99.6% (CI, 100 – 101), administer heparin doses in boluses vs 0.4% (CI, -0.3 – 1.3) who administer the dose in a continuous infusion of heparin.

After reviewing the existing medical literature and knowing the different factors that could cause variability in the ACT values, factors that were associated in the study conducted by Junko Ichikawa et al. where patients who reached the target ACT values were those with the highest platelet count, researchers acknowledge the popularity of the method of bolus dose administration when routine clinical practice interventions are individualized in each procedure, evaluating each patient's response dose and considering different situations regarding platelet count, hypothermia, and excess volume, among others. However, the study conducted by Santos J. et al. compares heparin administration in continuous infusion vs in bolus concluding that the continuous infusion technique contributes more stable anticoagulation with ACT values within optimal ranges suggesting that a clinical trial should be conducted to contribute more to these theories since there are no more publications on this topic.[2,22]

When studying heparinization methods in obese patients, (Chart 5), 68.1% (CI, 62.5 – 73.4) of respondents use the same heparin dose calculation formula for all the patients while 16.3% (CI, 11.8 – 20.7) do the calculation based on lean weight unlike 7.8% (CI, 4.5 – 10.9) who administer doses based on the body mass index (BMI) while the remaining 7.8% (CI, 4.5–10.9) heparinize obese patients considering different characteristics such as sex, temperature, circulatory arrest. Studies like the one

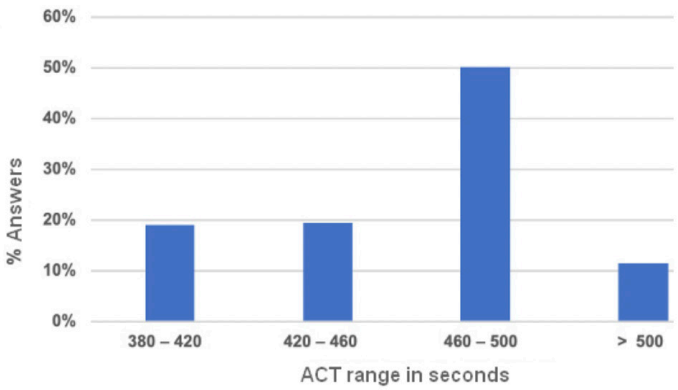

Chart 3. ACT range considered optimal for using ECC.

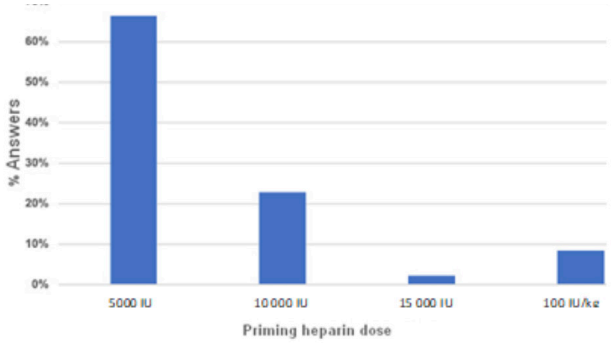

Chart 4. Dose of heparin used to prime the extracorporeal circuit.

conducted by Mya S. Baker et al. show a reduction of heparin requirements in overweight patients when they use doses based on lean body mass for "systemic," heparinization.[23]

To this date, the medical literature available has not published a study on heparin dose for obese patients "during ECC". However, the research conducted by Matías Vienne et al. describes the efficacy of heparinization carried out with dose calculation adjusted to the ideal body weight of obese patients in whom it is estimated that there is a reduction of heparin dose and, consequently, this prevents overdosing in this population.[24] The results obtained with this survey show that there is great interest in our region in optimization and individualization of heparinization for obese patients, perhaps due to the increase of the obese population in Latin America along with the growing interest by active perfusionists to remain updated and upgrading the quality of ECC management according to evidence-based perfusion.

The difference in the production and origin of heparin marked by the FDA from 2009 onwards is associated with the different doses used in Latin-American countries to reach the same ACT values in patients that undergo ECC. Regarding management of heparin brands (Chart 6) used by perfusionists at their working places, 48.3% (CI, 42.2 – 54.3) of the respondents only have one brand, 37.4% (CI, 31.5– 43.2) have two, 9.1% (CI, 5.8– 12.5) have three, and 5.3% (CI, 2.5 –7.9) have more than three brands available.

A study conducted by Ríos et al. that compared the efficacy of three brands on unfractionated heparin used in ECC revealed that one of them has superior effects and reached optimal ACT levels in 60% of patients after the systemic dose was administered compared to the 30% reached by other brands included in the study.8 More studies like that are required to identify the heparin brands that have the greatest efficacy power in patients that undergo ECC.

In patients that undergo circulatory assistance or ECMO, a heparin continuous infusion system is used that makes it possible to maintain more stable levels of anticoagulantion. Currently, perfusionists from Latin America wait until the ACT levels drop before administering heparin boluses in the ECC circuit. As we can see on Chart 7, 57.1% (CI, 50.9 –62.9) of the respondents added 5000 to 10 000 IU of heparin to the circuit, 27.4% (CI, 22.1– 32.9) added 100 IU/kg, (so this formula behaves as the increasing trend to replace this deficit), 13.9% (CI, 9.7– 18.1) added 2500 IU, and 1.1% (CI, 0.1–2.4) added 10 000 IU to 15 000 IU. One person said that he added no heparin to the circuit whatsoever.

The study conducted by Santos J. et al. that compared bolus heparin administration vs continuous infusion demonstrated that after connecting a direct infusion system of the anticoagulant to the circuit, they managed to maintain more stable, constant heparin levels while the patient was connected to the ECC machine.[2]

Regarding heparin management when ECC is finishing and the ACT result is below the optimal level almost half the respondents (45.5%) did not administer heparin to the circuit, 29.1% added 2500 IU or less, 17.9% added 5000 IU to 10 000 IU while 7.5% added 100 IU/kg (Chart 8). It is important to consider how much below the optimal level the ACT result is since depending on how low it is that is how the risk of activating hemostasis will be. In addition, it is safer to maintain optimal levels until the pump is out and, therefore, be prepared in case a situation comes up where pump time prolongs or if after the pump is out,

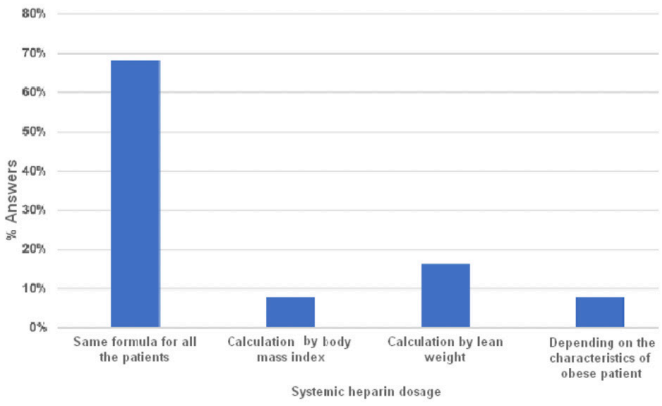

Chart 5. Systemic heparinization strategy for obese patients.

it is necessary to restore extracorporeal circulation (Evidence level C).

To treat suspected heparin resistance, 82.7% of the perfusionists surveyed used fresh frozen plasma, 4.9% used antithrombin III, another 4.5% used human albumin, 1.1% used hirudin, and 6.8% used another type of method (Chart 9). It is evident in this study that there is a high percentage of fresh frozen plasma administration, but there are no studies that show its greater efficac. Also, evidence is based on experts' opinions, probably its use has to do with its low cost and its wide availability as opposed to other options.

Although it is true that heparin exerts its anticoagulant action through the stimulation of ATIII activity, this property is present in just one third of heparin molecules.[5] Their negative charges bind them in a non-specific manner to different plasma proteins, which reduces the number of heparin molecules available to combine with ATIII.[25] Therefore, we should mention that some cases of heparin resistance can be due to increased factor VIII/von Willebrand factor complex or an increased factor VIII independently, and also cases of thrombocytosis where there is more availability of platelet factor 4 considering that heparin resistance is due to the fact that is it is bound to other proteins and is not due to a Antithrombin III deficiency as it is believed.[26,27] Concentration of these specific protein-ligand complexes varies from one person to the next. This explains the variability of the anticoagulant effect obtained on equal doses in different people. In these cases, the only choice is to administer more heparin.[28,29]

Results show that using hirudin as an alternative is not common, probably because usual changes in the techniques have to be taken into account because they have short duration and high cost limits its use.

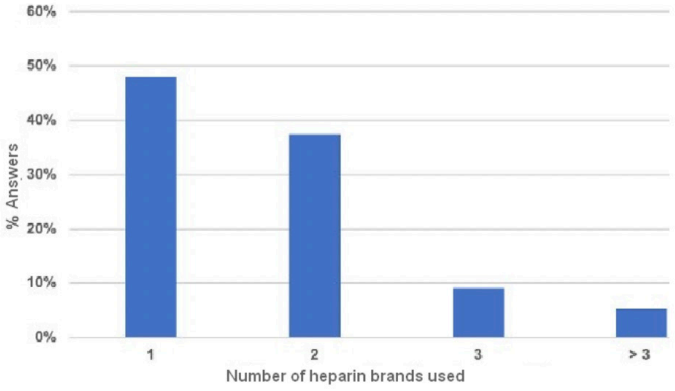

Chart 6. Number of heparin brands used at their working place.

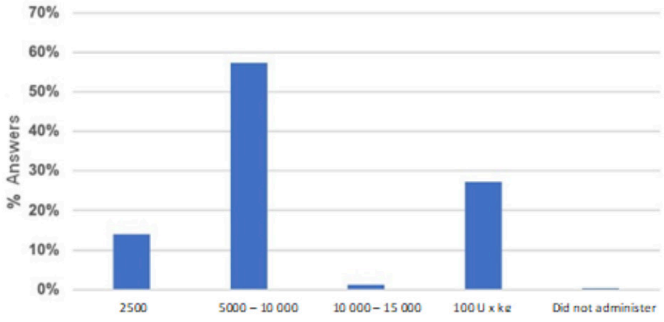

Chart 7. Dose of heparin administered with reduced ACT values during ECC.

Regarding the machines used to monitor anticoagulation, 45.4% of the perfusionists surveyed use ACT Plus (Medtronic Parkway Minneapolis, United States) to monitor anticoagulation, 33.5% use Hemochron Response (Accriva Diagnostics Inc. San Diego, United States), 6.7% use Hemochron Jr. Signature Elite + (ACT+) (Accriva Diagnostics Inc. San Diego, United States) while 5.6% use the i-STAT system (Abbot Laboratories, Chicago, United States) (Chart 10)

ACT measurement machines are the equipment of choice and the only tool to make decisions in the beginning, to maintain and reverse anticoagulation, in addition to some criteria for decision-making process to transfuse blood derivatives during or after cardiovascular surgery in Latin America.

Although ACT is a global test that takes into account many variables, its result are not always an indication that good anticoagulation or antithrombotic status has been achieved. There are several schools with different protocols for the management of heparin-protamine doses. However, studies

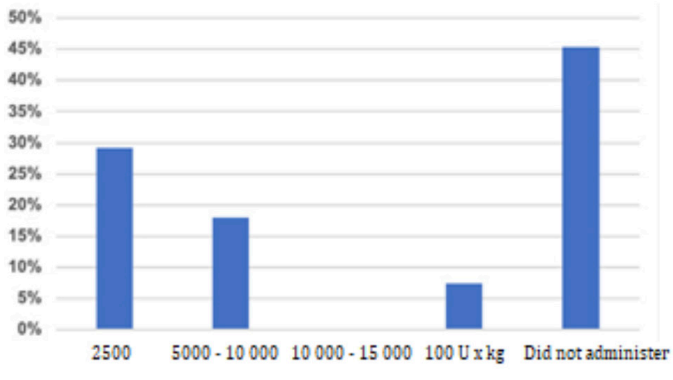

Chart 8. Dose of heparin administered with reduced ACT values when close to finishing ECC.

have demonstrated that individualizing the heparin dose, maintaining specific levels for each patient during ECC, adjusting and individualizing its reversion with protamine, and its dose based on the actual levels of circulating heparin and not on the early dose reduces significantly the use of blood derivatives and its comorbidities. Heparin, as any other drug, has its own half-life and its power varies based on many effects inherent to ECC. Excess doses will cause post-ECC alterations and very low doses will lead to the production of thrombin and consumption of coagulation factors. Protamine outside the therapeutic dose also has direct effects on factors such as IX and VII causing even anticoagulant effects that can be observed even 24 hours after its administration.

All of this leads us to wonder whether measuring ACT is enough for the adequate management of anticoagulation or whether it would be better to use additional pieces of equipment to measure heparin titration based on a dose-response test like the HMS/HepCon machine (Medtronic, Minneapolis, MN, United States.) or other similar machines. The utility of viscoelastic tests could also be assessed to acquire more data and make more accurate decisions depending on the surgical moment.[30]

One of the advantages of using heparin during ECC is the possibility of reversing its effect through the use of protamine. There are several methods to reverse the effect of heparin, among the traditional ones, estimating the dose protamine based on the patient's weight and the total heparin dose administered. According to the anticoagulation guidelines during ECC published by the Thoracic Surgeons Society, the Cardiovascular Anesthesiologists Society, and the American Society of Extracorporeal Technology, it is recommended to estimate the protamine reversion dose based on the titration of the circulating heparin level, since this technique has been associated with less bleeding, and use of blood derivatives (Recommendation IIa, Evidence level B).[16]

However, in our region not all centers have the possibility of performing heparin titration at the patient's bedside and that is why the most widely used method is the one based on the administration of the total heparin dose. In our study, 53.2% used the 1:1 ratio (Chart 11), 20.6% considered the use of 0.8:1 ratios, 13.6% 1:1.2 ratios, and 12.5% the use of 1:1 ratios.5 These values fall within the recommended ranges (Recommendation IIa, Evidence Level C) in the clinical practice guidelines that recommend not exceeding the 1:2 ratio.6 since it can cause inhibition of platelet function and increase risk of bleeding (Evidence Level C).14 Specifically, Mochizuki et al. showed increased ACT values when reversion ratios > 1:2.6 of protamine were used.[31]

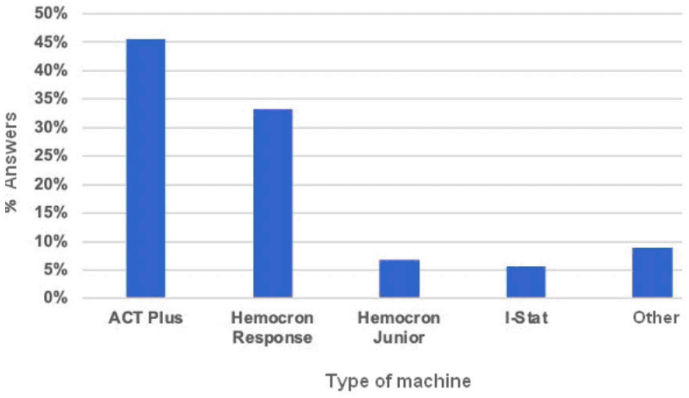

Chart 10. ACT measurement piece of equipment used.

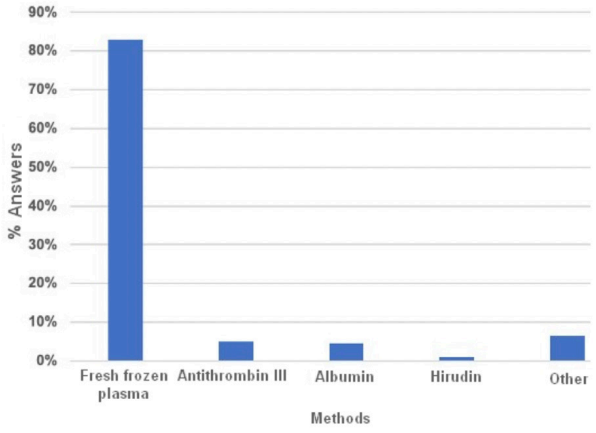

Chart 9. Method used to treat suspected heparin resistance.

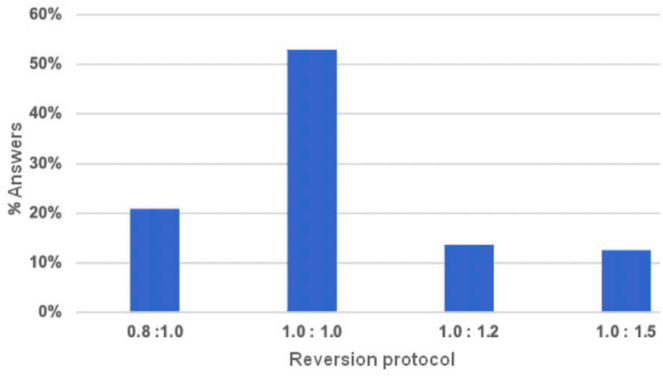

Chart 11. Heparin reversal with protamine sulfate.

CONCLUSIONS

Based on the results obtained through the survey conducted, we can conclude that regarding the strategies used for heparinization and monitoring anticoagulation in adult patients including the management of obese patients undergoing ECC, the trend in Latin America is to administer a systemic heparin dose of 300 IU/kg and add 5000 UI during the priming to reach ACT cut-off value of 460-500 s. Respondents considered this cut-off value optimal to use ECC. The time waited to take the ACT sample was 3 min and the tool that is most frequently used to measure this ACT is ACT Plus by Medtronic. Regarding management during ECC, if ACT is below its optimal level, 5000 IU to 10 000 IU of heparin are administered as a bolus and if this happens when ECC is finishing, no heparin is administered. If heparin resistance is suspected, the trend is to administer fresh frozen plasma. To revert the effect of heparin, protamine is used in a 1:1 ratio.

When evaluating the behavior of the answers analyzed, we can conclude that in Latin America there are several strategies for heparinization and anticoagulation monitoring. It is clear that there is a more homogeneous trend regarding anticoagulation monitoring strategies during ECC.

Regarding future studies, we should analyze these trends and discrepancies since they contribute valuable information. On the other hand, they encourage greater research in the area of anticoagulation management in ECC, which would promote the creation of protocols based on Latin-American scientific evidence.

LIMITATIONS

The researchers believe that the impact of these results obtained from the survey could have been greater had the the Southeastern region of Brazil been included. This was not possible due to language barrier.

Another limitation was the perfusionists' willingness to answer the survey questions, or rather do it in a hesitant manner out of fear of answering it the wrong way. Among the limitations we include the wide variety of values considered optimal, questions with the option to select more than one answer, and finally the fact that it was not mandatory to answer all the questions without omitting any of them.

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