



Observational Safety Study of Clottafact® Fibrinogen Concentrate: Real-World Data in Mexico

Ignacio Colin-Bracamontes¹ · Ángel Augusto Pérez-Calatayud² · Raúl Carrillo-Esper³ · Ernesto Rodríguez-Ayala⁴ · Misael Padilla-Molina⁵ · Alejandro Posadas-Nava⁶ · Susana Olvera-Vázquez⁷ · Lidia Hernández-Salgado⁸

Published online: 25 March 2020
© The Author(s) 2020

Abstract

Background and Objective The use of fibrinogen concentrate to treat or prevent major bleeding with regard to potential adverse reactions has not been free of controversy. Our objective was to perform a post-authorization safety study to describe the use of Clottafact® (LFB Biomedicaments) fibrinogen concentrate in real-life medical practice in Mexico.

Methods This was a prospective, observational study that collected and evaluated information between January 2017 and June 2019 related to suspected serious adverse reactions (SUSARs) during and after Clottafact® infusion.

Results Information from 40 subjects was analyzed; 43% were women (n = 17), mean age was 39.05 ± 26.8 years (range 0–91 years). The medical specialties included in this analysis were cardiac surgery – 52.5% of the cases, gynecology/obstetrics – 17.5%, general surgery and orthopedics – 12.5% each, and hematology and neurosurgery – 2.5%, respectively. Mean plasma fibrinogen levels before and after Clottafact® infusion were 2.58 g/L and 4.02 g/L; *p* = 0.001, respectively. The mean Clottafact® dose was 2.20 ± 0.77 g. One patient presented SUSARs (dry mouth and dysgeusia) with drug administration, which ceased after treatment discontinuation.

Conclusions In this real-life post-marketing study, the safety profile of Clottafact® was very similar to previous reports. Thus, Clottafact® shows a favorable safety profile in clinical practice.

Key Points

Clottafact® showed a favorable safety profile in clinical practice in Mexico.

Clottafact® human fibrinogen concentrate usage profile is considered safe in real-world conditions for the treatment of acquired or congenital fibrinogen deficiency.

✉ Dr. Ignacio Colin-Bracamontes
ignacio.colin@gmail.com

¹ LFB Mexico and Anahuac Mexico University, 243 Paseo de la Reforma Avenue, Floor 23, 06500 Mexico City, Mexico

² Intensive Therapy Unit/Children in Mexico's General Hospital, Mexico City, Mexico

³ Mexican Academy of Surgery, National Rehabilitation Institute, Mexican Group for the Intensive Medicine Study, National Academy of Medicine, Mexico City, Mexico

⁴ Anahuac Mexico University, Huixquilucan, Mexico City, State of Mexico, Mexico

⁵ Council for Gender Equality, Chihuahua, Mexico

⁶ High Specialty Medical Unit of Obstetrics and Gynecology, IMSS, Mexico City, Mexico

⁷ Strategy and Regulatory Science, LFB Mexico, Mexico City, Mexico

⁸ Pharmacovigilance Coordination Department, Innovare R&D, Mexico City, Mexico

1 Introduction

Fibrinogen has a functional role as the fibrin polymer precursor for the enzymatic process of coagulation [1]. The severity of coagulation disorders frequently depends on the circulating fibrinogen levels. This is a glycoprotein with a molecular weight of 340 KDa, which is synthesized in the liver and has plasma concentrations between 1.5 and 3.5 g/L. In some cases, such as in pregnancy, baseline levels may be higher [1].

Fibrinogen disorders may be caused by congenital or acquired defects. Clinical presentations vary significantly,

with some causing severe bleeding episodes or even perinatal complications [1]. Congenital defects can be classified by the circulating fibrinogen quantity (hypofibrinogenemia and afibrinogenemia) or quality (dysfibrinogenemia). The main afibrinogenemia symptom is bleeding, while patients with low hypofibrinogenemia may be generally asymptomatic [3]; nevertheless, patients still have a high risk of complications, particularly in trauma, cardiovascular surgery, and obstetric surgery [4]. In cases of obstetric hemorrhage with circulating levels < 2 g/L, there is a 100% positive predictive value of progression to severe postpartum hemorrhage [5]. In developing countries, bleeding during childbirth is the major cause of maternal mortality. It also causes significant morbidity in developed countries. There are many international guidelines for the management of severe postpartum hemorrhage in patients with coagulopathies [6–9]. The use of hemostatic drugs and devices such as the blood-clotting analyses (TEG or ROTEM) can be considered for goal-guided active management. It is generally accepted that the core issue of coagulopathy is hypofibrinogenemia, because low fibrinogen levels are associated with a qualitative and quantitative deficiency in clot formation. Fibrinogen concentrate has been used to correct hypofibrinogenemia during postpartum hemorrhage and is accepted as part of active bleeding management [10].

Post-traumatic bleeding is one of the leading causes of death around the world [11]. This bleeding is considered preventable if there is adequate and timely treatment [12]. Cardiac surgery is associated with perioperative bleeding, with an increase in hospitalization time and mortality [4, 13].

The replacement of fibrinogen in hemorrhage can be implemented with fresh frozen plasma, cryoprecipitates, and/or fibrinogen concentrate [14]. Human fibrinogen concentrate is considered the treatment of choice for fibrinogen replacement in patients with congenital deficiency and is an effective alternative when there is limited access to cryoprecipitates [7, 15].

In Mexico, the use of fibrinogen concentrate (Clottafact®) has been approved and used since 2015, with the broad indication of acquired and congenital fibrinogen deficiencies. It is available as a lyophilized powder with 1.5 g of fibrinogen dissolved in 100 mL of sterile water for infusion [16]. While its clinical utility is clear, the use of fibrinogen concentrate to treat or prevent major bleeding is controversial due to the potential adverse effects. Therefore, the main objective of this research was to study the safety of Clottafact® fibrinogen concentrate in real-world conditions in Mexico, and to monitor adverse events.

It should be noted that six fibrinogen congenital deficiency patients in another study had adverse reactions associated with Clottafact®, including headache and night sweats. Patients may also have anaphylactic allergic reactions to any protein-derived and intravenous products. Due

to the mechanism of action of fibrinogen concentrate, the following reactions also cannot be excluded: thrombosis, transient hypotension, chills, and hyperthermia [28].

2 Subjects and Methods

This safety study, which was performed after the authorization of Clottafact® fibrinogen concentrate (FC), was observational, prospective, and multicenter. The primary objective was to collect information about suspected serious adverse reactions (SUSARs) during and after administration of Clottafact® human fibrinogen concentrate, as well as to perform a causality assessment of SUSARs. Secondary objectives included gathering data regarding which medical specialties tend to use FC, the clinical reasoning behind treatment with FC, the SUSARs associated with its use, and the states where patients tended to be treated with FC within Mexico. It is important to mention that this is an early-stage post-commercialization study with the sole objective of assessing the safety, not efficacy, of the product.

The collection of SUSAR information was reported by the treating physicians. These physicians agreed to be part of this study and were trained in the proper completion of the SUSAR report format. This information was then used to develop a pharmacovigilance safety assessment for Innovare R&D. These reports recorded the patients' date of birth, sex, home state, the indication for the use of FC, the dose of FC administered, concomitant medications, and the clinical manifestations and prognosis of SUSARs. With regard to thromboembolic risk assessment, physicians were allowed to perform whichever studies they found pertinent in order to mitigate this potential risk. However, Doppler ultrasounds were not conducted in any of the study patients.

The SUSARs were registered using the Medical Dictionary for Regulatory Activities (MedDRA) 22.0 version [17]. They were classified as serious or non-serious. Serious SUSARs included death, life-threatening events requiring hospitalization, disability or incapacity, congenital abnormality/birth defect, or other medically important conditions. Subsequently, there was a review on the duplicity of cases that were reported as SUSARs. In order to consider the causality of an FC adverse reaction, the following were noted: the temporality from the beginning to the end of the treatment; the severity classified according to the intensity of a clinical manifestation as mild, moderate, or severe; concomitant treatments; and information about co-morbidities that was obtained from the medical history with regard to information recorded in this study such as medical procedures, relevant gynecological and obstetric history, non-pathological and pathological personal history, and hereditary background.

The inclusion criteria for this study were patients who were prescribed Clotfact[®] for indications by their treating physician, who agreed to sign the informed consent in order to report safety information on a case-by-case basis. The exclusion criteria were patients with hypersensitivity to FC or to any of its components, or physicians who did not provide informed consent.

There are no data recorded concerning the physicians who declined to consent to their participation in this study.

2.1 Statistical Analysis

Descriptive statistics were performed according to the measurement level of the variables. Quantitative variables are expressed as mean, standard deviation, median, interquartile range (IQR), and minimum and maximum. The chi-square test was used to contrast the equal proportions hypothesis. Student's t-test for related samples was used to compare the mean of laboratory values when the data demonstrated a normal distribution, and the Wilcoxon test was used when there was not a normal distribution. A *p* value < 0.05 was deemed statistically significant. The analyses were performed using SPSS v25.0 (SPSS Inc., Chicago, IL, USA).

3 Results

In this multicenter study, 40 patients from nine hospitals were recruited between January 2017 and June 2019: there were 23 men (57%) and 17 women (43%). The mean age was 39.05 ± 26.8 years, median 37 years (interquartile range (IQR): 16–63 years), range 0–91 years. Mean weight and height were 55.1 ± 28.4 kg and 145.9 ± 37.5 cm, respectively. The mean Clotfact[®] dose was 2.20 ± 0.77 g. In this study there were 13 pediatric patients (median age 11 years) with a median dose of 1.5 g (IQR: 1.5–2.25 g). Complete blood count (CBC) and clotting times were performed on hospital admission and discharge. Before and after Clotfact[®] infusion, the mean plasma fibrinogen levels were 2.58 g/L and 4.02 g/L; *p* = 0.001, respectively. No significant differences were found between hemoglobin, hematocrit, and platelet levels on hospital admission and discharge. The average prothrombin time was 14.75 s on hospital admission and 14.85 s on hospital discharge (*p* = 1.000) (Table 1). It is important to highlight that discharge lab panels are relevant to this safety study because the half-life of Clotfact[®] is quite similar to that of endogenous human fibrinogen. Clotfact[®] has a similar pharmacokinetic profile to that of its naturally occurring

Table 1 Laboratory values on hospital admission and discharge in the studied population

Variable	Hospital admission	Hospital discharge	<i>p</i> value
Hemoglobin			
Mean (SD), g/dL	12.14 (3.97)	10.76 (2.28)	0.212
Median (IQR), g/dL	12.20 (9.90–14.75)	11 (8.60–12.70)	
Hematocrit			
Mean (SD), %	36.66 (12.6)	32.21 (7.75)	0.113
Median (IQR), %	36 (28.90–44.95)	31.20 (25.15–37.85)	
Platelets			
Mean (SD), billions/L	182.55 (108.91)	193.28 (121.88)	0.913
Median (IQR), billions/L	159 (103–237)	162 (123.5–240.7)	
Fibrinogen			
Mean (SD), g/L	2.58 (2.77)	4.02 (1.77)	0.001
Median (IQR), g/L	2.38 (2.0–2.8)	3.0 (3.0–4.3)	
Prothrombin time			
Mean (SD), seconds	14.75 (3.94)	14.85 (3.83)	1.000
Median (IQR), seconds	14.45 (10.73–19.18)	15.15 (11.03–18.38)	
Thromboplastin partial time			
Mean (SD), seconds	34.01 (11.27)	30.54 (10.55)	0.144
Median (IQR), seconds	29.50 (27.10–39.40)	30.30 (21.95–39.25)	
INR			
Mean (SD)	1.26 (0.21)	1.28 (0.26)	0.157
Median (IQR)	1.32 (1.02–1.40)	1.30 (1.03–1.52)	

INR international normalized ratio, IQR interquartile range, SD standard deviation

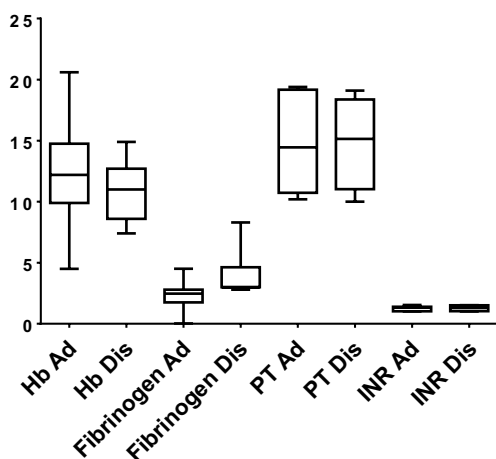


Fig. 1 Distribution and variation of laboratory values on hospital admission and discharge in the studied population. *Ad* admission, *Dis* discharge, *Hb* hemoglobin, *PT* prothrombin time, *INR* International Normalized Ratio. *First whiskers (from bottom to top)*: each one represents interquartile 1 referring to the first 25% of the whole data of a variable. *First boxes (from bottom to top)*: each one represents interquartile 2 referring to the second 25% of the whole data of a variable. *Second boxes (from bottom to top)*: each one represents interquartile 3 referring to the third 25% of the whole data of a variable. *Second whiskers (from bottom to top)*: each one represents interquartile 4 referring to the fourth 25% of the whole data of a variable

molecule. The distribution and variation of some of the laboratory values regarding hospital admissions and discharges of the studied population are shown in Fig. 1.

This study included patients from the following Mexican states: Mexico City, 28 patients (70%); Queretaro, seven patients (17.5%); Puebla, three patients (7.5%); Nuevo Leon and State of Mexico, one patient each (2.5%).

The medical specialties that used Clottafact[®] and contributed information for these analyses were cardiac surgery – 52.5% of the cases (21 patients),

gynecology/obstetrics – 17.5% (seven patients), general surgery – 12.5% (five patients), orthopedics and trauma – 12.5% (five patients), and hematology and neurosurgery—2.5% each (one patient each). Age at treatment initiation and gender per medical specialty are shown in Table 2.

The causes of bleeding were divided according to the MedDRA classification into three levels of hierarchy. This classification includes System Organ Class (SOC), Grouped Terms (High-Level Terms (HLT) and High-Level Group Terms (HLGT)), and Preferred Terms (PT). Within the SOC level, traumatic injuries, intoxications, and complications on therapeutic procedures had the highest frequency of bleeding with 67.5% (27 patients), followed by pregnancy, postpartum, and perinatal diseases with 12.5% ($n=5$), and hepatobiliary disorders with 7.5%. Two patients had vascular disorders (5%), one had a heart disorder (2.5%), and one had a gastrointestinal disorder (2.5%). There was only one patient (2.5%) with congenital inherited disorders (Table 3), thus the percentage of congenital versus acquired deficiency was 2.5% and 97.5%, respectively.

It is important to mention that throughout the study no thrombotic events were reported.

3.1 Safety Assessment

Only one patient reported SUSARs during the study period. The patient was a 65-year-old woman weighing 55 kg with congenital hypofibrinogenemia. She experienced dry mouth and dysgeusia 6 days after the onset of FC administration. The treatment was discontinued 8 days later, at which point suspected adverse reactions to the medication ceased. Concomitant medications were aspirin, clopidogrel, tramadol, gabapentin, and linezolid. At the end of the monitoring period, the treating physician concluded that the overall outcome was favorable for the patient, as the symptoms

Table 2 Medical specialties that used fibrinogen concentrate

Variable	Heart surgery $n=21$	Gynecology/obstetrics $n=7$	General surgery $n=5$	Orthopedics and trauma $n=5$	Hematology $n=1$	Neurosurgery $n=1$
Gender						
Female, n (%)	8 (38.1)	7 (100)	0 (0)	1 (20)	1 (100)	0 (0)
Male, n (%)	13 (61.9)	NA	5 (100)	4 (80)	0 (0)	1 (100)
Age at start of treatment						
Mean (SD), years	34 (29.4)	29.3 (8.3)	58.3 (35.9)	49.3 (11.3)	65	59
Minimum–maximum, years	0–79	18–41	10–91	37–63		
Co-morbidities						
Yes, n (%)	20 (95.2)	6 (85.7)	5 (100)	3 (60)	1 (100)	1 (100)
No, n (%)	1 (4.8)	1 (14.3)	0 (0)	2 (40)	0 (0)	0 (0)

SD standard deviation

Table 3 Causes of bleeding as classified according to the terms of the Medical Dictionary for Regulatory Activities (MedDRA) [*N* = 40]

Classification according to MedDRA	Value [<i>n</i> (%)]
<i>System Organ Class (SOC)</i>	
Pregnancy, postpartum, and perinatal diseases	5 (12.5)
Traumatic injuries, intoxications, and complications on therapeutic procedures	27 (67.5)
Heart disorders	1 (2.5)
Congenital and genetical disorders	1 (2.5)
Gastrointestinal disorders	1 (2.5)
Hepatobiliary disorders	3 (7.5)
Vascular disorders	2 (5)
<i>Group Terms (HLT and HLG T)</i>	
Liver abscess	1 (2.5)
Pulmonary atresia	1 (2.5)
Complications of liver transplant	2 (5)
Hemorrhage of digestive tract	1 (2.5)
Hemorrhage during surgery	3 (7.5)
Hemorrhage during pregnancy	1 (2.5)
Postpartum hemorrhage	1 (2.5)
Congenital hypofibrinogenemia	1 (2.5)
Multiple traumatic injuries	3 (7.5)
Traumatic injury	1 (2.5)
Placenta accreta	3 (7.5)
Post-surgery bleeding	20 (50)
Hypovolemic shock	2 (5)
<i>Preferred Terms (PT)</i>	
Liver abscess	1 (2.5)
Pulmonary atresia	1 (2.5)
Complications of liver transplant	2 (5)
Factor I deficit	1 (2.5)
Hemorrhage during pregnancy	2 (5)
Gastrointestinal hemorrhage	1 (2.5)
Hemorrhage at medical procedure	3 (7.5)
Postpartum hemorrhage	1 (2.5)
Post-procedure hemorrhage	20 (50)
Multiple traumatic injuries	3 (7.5)
Injury	1 (2.5)
Placenta accreta	2 (5)
Hypovolemic shock	2 (5)

HLGT high-level grouped terms, *HLT* high-level terms

associated with the drug disappeared with treatment discontinuation. It was also considered that clopidogrel is known to cause taste alterations and that it may have been a factor in the dysgeusia. Furthermore, it is unknown if the concomitant medications were discontinued. Based on the available information, the market authorization holder (MAH) assessed the relationship between dysgeusia and Clottafact®

as “possible” according to the World Health Organization causation method.

4 Discussion

The safety profile of fibrinogen concentrate was evaluated in 40 study subjects. Only one patient reported adverse events. Both adverse events (dry mouth and dysgeusia) were considered non-serious. Causation of the adverse events by Clottafact® was potentially confounded by the concurrent use of clopidogrel, though both symptoms ceased after treatment discontinuation. Therefore, this is key evidence in considering causality associated with the study drug. There were no reports of deaths, thrombotic events, or allergic reactions related to treatment. These findings are consistent with other reports that have demonstrated a low rate of adverse events following FC use [2, 18]. Consequently, we conclude that an infusion with Clottafact® is well tolerated, as Clottafact® use during the course of the study was free of SUSARs in 39 of the 40 included patients.

This study reports data regarding Clottafact® FC use in real clinical practice in Mexico. Here we report that one of the indications for FC use was postpartum hemorrhage (PPH), which is consistent with studies demonstrating that patients with low fibrinogen levels have a higher risk of developing PPH. During PPH, fibrinogen levels decrease rapidly because of the consumption of coagulation factors and blood loss [5]. In recent years, fibrinogen has been routinely used in PPH because it produces less hemodilution and is more rapidly available than fresh frozen plasma (which involves a waiting time for the defrosting process) [5, 7]. The lowest limit of fibrinogen plasma concentrations in which FC should be used during PPH is not yet well established, but 3 g/L or higher is considered to be sufficient; it has been demonstrated that regardless of other laboratory results, the risk of developing severe PPH with fibrinogen levels below 2 g/L increases up to 11 times [5, 7]. It is not recommended that treatment initiation be delayed for laboratory results during active hemorrhage; instead, immediate transfusion of blood components, FC, and/or procoagulants should be carried out [6]. Fibrinogen levels decrease even more quickly than other coagulation parameters during the early stages of trauma [19].

In our study, cardiac surgery was the medical specialty with the highest frequency of FC use. Its administration has been accepted in patients who undergo cardiac surgical interventions and have active bleeding either during the intervention or afterwards [20, 21] because its use is not associated with increased mortality, but rather offers risk reduction for hemorrhagic complications [20]. The safety and efficacy of FC use has also been demonstrated in the

treatment of bleeding for pediatric patients who undergo complex cardiac surgeries [22].

Thrombosis is one of the most serious, but uncommon, reported adverse events involving FC use when treating afibrinogenemia [18], as it is assumed that administration could precipitate activation of coagulation [23]. However, there were no reports of thrombosis in our study.

The use of FC is considered safe for the treatment of hypofibrinogenemia, afibrinogenemia, or dysfibrinogenemia [24, 25]. It is worth noting that there are several advantages of FC use compared to cryoprecipitates, including its purity, plasma-derived virus inactivation, lower hemodilution, quality concentration, and higher fibrinogen concentrations compared to other blood-derived products [25]. Likewise, it has been observed that FC is more effective and acts faster than a fresh frozen plasma/platelets cycle [26].

This study assessed the clinical reports of 40 patients with various causes of bleeding due to fibrinogen deficiency (congenital or acquired). The sample size of our study, while seemingly small, can be considered sufficiently representative with respect to patients with afibrinogenemia or hypofibrinogenemia due to the rarity of these conditions (frequency of congenital fibrinogen is approximately 1 out of 1,000,000 individuals). Moreover, the sample size of our study is much larger than previous publications, with reports of up to 14 individuals [27]. That said, FC has been commercialized for both congenital and acquired indications in Mexico since 2016 (compared to other countries where its use has been widespread for decades).

5 Conclusion

In conclusion, based on this real-life experience in Mexico, the Clottafact® human FC usage profile is considered to be safe for real-world conditions in the treatment of acquired or congenital fibrinogen deficiencies in the Mexican population.

Acknowledgements The authors acknowledge the input by Dr. Sami Zitouni, Nathalie Scour, Aurelie Perrot, Nora Alicia Coronado, and the LFB Mexico sales force, Caitlin Pray and Alejandro Carrillo-Villegas.

Author Contribution All authors took part in the conception and design of the work. Material preparation, data collection, and analysis were performed by Dr. Ignacio Colin-Bracamontes, Lidia Hernández-Salgado, and Dr. Ernesto Rodríguez-Ayala. The writing, review, and editing of this work were performed by Dr. Ignacio Colin-Bracamontes and Lidia Hernández-Salgado. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Funding Funding was provided by the Pharmaceutical Laboratory LFB Mexico, SAPI de CV.

Conflict of interest IC and SO are full-time employees at the Pharmaceutical Laboratory LFB Mexico, SAPI de CV. LH is a full-time employee at Innovare R&D in the Pharmacovigilance Coordination Department. AC, RC, MP, and AP are currently speakers for LFB Mexico, but no further conflicts of interest have been established.

Ethics Approval This study was performed in compliance with Good Clinical Practices, the 1964 Helsinki Declaration and its amendments, and with the national regulations in force. The Nuremberg Code of Ethics was also followed. The study is considered as a minimal risk research. Following the ethical standards of the National Pharmacovigilance Committee, this study and its written consent were evaluated and approved under the code CNFV/PCT/145/2014.

Informed consent Written consent was approved by all participating physicians who reported safety information for the elaboration of this study.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

1. Tiscia GL, Margaglione M. Human Fibrinogen: Molecular and Genetic Aspects of Congenital Disorders. *Int J Mol Sci.* 2018;19(6):1597.
2. Ross C, Rangarajan S, Karimi M, Toogeh G, Apte S, Lissitchkov T, Acharya S, Manco-Johnson MJ, Srivastava A, Brand B, Schwartz BA, Knaub S, Peyvandi F. Pharmacokinetics, clot strength and safety of a new fibrinogen concentrate: randomized comparison with active control in congenital fibrinogen deficiency. *J Thromb Haemost.* 2018;16(2):253–61.
3. Neerman-Arbez M, Casini A. Clinical Consequences and Molecular Bases of Low Fibrinogen Levels. *Int J Mol Sci.* 2018;19(1):192.
4. Négrier C, Ducloy-Bouthors AS, Piriou V, De Maistre E, Stieltjes N, Borel-Derlon A, Colson P, Picard J, Lambert T, Claeysens S, Boileau S, Bertrand A, André MH, Fourrier F, Ozier Y, Sié P, Gruel Y, Tellier Z. Postauthorization safety study of Clottafact®, a triply secured fibrinogen concentrate in acquired fibrinogen deficiency: a prospective observational study. *Vox Sang.* 2018;113(2):120–7.
5. Cortet M, Deneux-Tharaux C, Dupont C, Colin C, Rudigoz RC, Bouvier-Colle MH, Huissoud C. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *Br J Anaesth [Internet].* 2012;108(6):984–9.
6. Sentilhes L, Vayssière C, Deneux-Tharaux C, Aya AG, Bayoumeu F, Bonnet MP, Djoudi R, Dolley P, Dreyfus M, Ducroux-Schouwey C, Dupont C, François A, Gallot D, Haumonté JB, Huissoud C, Kayem G, Keita H, Langer B, Mignon A, Morel O, Parant O, Pelage JP, Phan E, Rossignol M, Tessier V, Mercier FJ, Goffinet F.

- Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). *Eur J Obstet Gynecol Reprod Biol* [Internet]. 2016;198:12–21.
7. IMSS. Diagnóstico y tratamiento del choque hemorrágico en obstetricia. Guía de Evidencias y Recomendaciones: Guía de Práctica Clínica. Mexico. Mexico City: Coordinación Técnica de Excelencia Clínica y Coordinación de Unidades Médicas de Alta Especialidad; 2017. Available from: <http://www.imss.gob.mx/sites/all/statics/guiasclinicas/162GER.pdf>.
 8. Kozek-Langenecker S. Clinical efficacy of fresh frozen plasma compared with coagulation factor concentrates for treating coagulopathy in patients with massive bleeding. *Med Intensiva*. 2016;40(6):371–3.
 9. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, De Robertis E, Faraoni D, Filipescu DC, Fries D, Haas T, Jacob M, Lancé MD, Pitarch JVL, Mallett S, Meier J, Molnar ZL, Rahe-Meyer N, Samama CM, Stensballe J, Van der Linden PJF, Wikkelsø AJ, Wouters P, Wyffels P, Zacharowski K. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. *Eur J Anaesthesiol*. 2017;34(6):332–95.
 10. Collis RE, Collins PW. Haemostatic management of obstetric haemorrhage. *Anaesthesia*. 2015;70(Suppl 1):78–86, e27–8.
 11. Satyam A, Graef ER, Lapchak PH, Tsokos MG, Dalle Lucca JJ, Tsokos GC. Complement and coagulation cascades in trauma. *Acute Med Surg*. 2019;6(4):329–35.
 12. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer EA, Ozier Y, Riddez L, Schultz A, Vincent JL, Spahn DR. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care*. 2016;20:100.
 13. Boer C, Meesters MI, Milojevic M, Benedetto U, Bolliger D, von Heymann C, Jeppsson A, Koster A, Osnabrugge RL, Ranucci M, Ravn HB, Vonk ABA, Wahba A, Pagano D. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth*. 2018;32(1):88–120.
 14. Pérez-Calatayud A, Anica-Malagón ED, Zavala-Barríos B, González-Hernández G, Carrillo-Esper R. Concentrado de fibrinógeno: una opción en el manejo de la hemorragia aguda. *Revista Mexicana de Anestesiología*; 39(2):300–304.
 15. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, Komadina R, Maegele M, Nardi G, Riddez L, Samama CM, Vincent JL, Rossaint R. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care*. 2019;23(1):98.
 16. Négrier C, Rothschild C, Goudemand J, Borg JY, Claeysens S, Alessi MC, Jaffry AC, Teboul C, Padrazzi B, Waegemans T. Pharmacokinetics and pharmacodynamics of a new highly secured fibrinogen concentrate. *J Thromb Haemost*. 2008;6(9):1494–9.
 17. ICH. Introductory Guide for Standardised MedDRA Queries (SMQs) Version16.0. March 2013. MSSO-DI-6226-16.0.0. Available from: https://www.meddra.org/sites/default/files/guidance/file/smq_intguide_16_0_english.pdf. Accessed 19 Mar 2020.
 18. Solomon C, Gröner A, Ye J, Pendrak I. Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data. *Thromb Haemost*. 2015;113(4):759–71.
 19. Hayakawa M, Gando S, Ono Y, Wada T, Yanagida Y, Sawamura A. Fibrinogen level deteriorates before other routine coagulation parameters and massive transfusion in the early phase of severe trauma: a retrospective observational study. *Semin Thromb Hemost*. 2015;41(1):35–42.
 20. Fassl J, Lurati Buse G, Filipovic M, Reuthebuch O, Hampf K, Seeburger MD, Bolliger D. Perioperative administration of fibrinogen does not increase adverse cardiac and thromboembolic events after cardiac surgery. *Br J Anaesth*. 2015;114(2):225–34.
 21. Rahe-Meyer N, Hanke A, Schmidt DS, Hagl C, Pichlmaier M. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: results from a randomized, placebo-controlled trial. *J Thorac Cardiovasc Surg*. 2013;145(3 Suppl):S178–85.
 22. Galas FR, de Almeida JP, Fukushima JT, Vincent JL, Osawa EA, Zeferino S, Câmara L, Guimarães VA, Jatene MB, Hajjar LA. Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: a randomized pilot trial. *J Thorac Cardiovasc Surg*. 2014;148(4):1647–55.
 23. Djambas Khayat C, El Khorassani M, Lambert T, Gay V, Barthez-Toullec M, Lamazure J, Bellon A, Henriot C, Bridey F, Négrier C. Clinical pharmacology, efficacy and safety study of a triple-secured fibrinogen concentrate in adults and adolescent patients with congenital fibrinogen deficiency. *J Thromb Haemost*. 2019;17(4):635–44.
 24. Ozier Y, Hunt BJ. Against: Fibrinogen concentrate for management of bleeding: against indiscriminate use. *J Thromb Haemost*. 2011;9(1):6–8.
 25. Erdoes G, Koster A, Meesters MI, Ortmann E, Bolliger D, Baryshnikova E, Ahmed A, Lance MD, Ravn HB, Ranucci M, von Heymann C, Agarwal S. The role of fibrinogen and fibrinogen concentrate in cardiac surgery: an international consensus statement from the Haemostasis and Transfusion Scientific Subcommittee of the European Association of Cardiothoracic Anaesthesiology. *Anaesthesia*. 2019;74(12):1589–600.
 26. Rahe-Meyer N, Sørensen B. For: Fibrinogen concentrate for management of bleeding. *J Thromb Haemost*. 2011;9(1):1–5.
 27. Négrier C, Rothschild C, Borg JY, Lambert T, Claeysens S, Sanhes L, Stieltjes N, Bertrand A, André MH, Sié P, Gruel Y, Tellier Z. Post-authorization safety study of Clotfact®, a triply secured fibrinogen concentrate in congenital afibrinogenemia. A prospective observational study. *Vox Sang*. 2016;111(4):383–90.
 28. Innovare R&D S.A. de C.V. Información para Prescribir Amplia de Clotfact®. Mexico City: Regulatory Affairs Department; 2018. Available from: Innovare R&D S.A. de C.V. 2018 internal document on file.