

Current Practice in FFP Preparation and Use in Greece: A National Survey

Yunanistan'da TDP Hazırlama ve Kullanımında Mevcut Uygulama: Ulusal Bir Anket

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Abstract

Objective: Fresh frozen plasma (FFP) transfusion is widely used in modern clinical settings. Practices regarding its use vary due to lack of guidelines from randomized trials. The aim of this study was to assess both the current practices regarding FFP production, use, and wastage and the implementation of quality control (QC), female donor plasma production policies, and use of pharmaceutical hemostatic agents in Greece.

Materials and Methods: The study was conducted during February–April 2018. For the first part of the study, data including FFP transfusion indication, hospital department, diagnosis, FFP units/transfusion episode, ABO compatibility, blood donor's sex, and reasons for discarding were collected. For the second part, questionnaire data were analyzed.

Results: According to data from 20 Greek hospitals, 12655 FFP units were transfused to 2700 patients during 5069 transfusion episodes in the studied period of time. Most patients were hospitalized in internal medicine, general surgery, and intensive care unit departments. Each patient received on average 4.69 units (2.5 units/episode). Transfusion requests were in accordance with international guidelines in 63.44% of cases and 99.04% of the units were given to ABO-identical patients. Main reasons for discarding included failure to meet quality requirements (30.06%), female donors (22.17%), and other causes (27.26%). Among 96.9% of all transfusion services across the country, 28.26% perform QC according to the directions of the European Directorate for the Quality of Medicines & Health Care and 68.83% discard plasma from female donors. Pharmaceutical hemostatic agents are used in 37.23% of the hospitals.

Conclusion: This is the first national survey regarding FFP production and transfusion in Greece. Staff of internal medicine, general surgery, and ICU departments, where most FFP-transfused patients are hospitalized, should be regularly involved in training on contemporary transfusion guidelines. Upcoming centralization of FFP production and inventory management could help in homogenizing practices regarding FFP use and improve product quality. Strengthening the use of pharmaceutical hemostatic agents could improve patients' management.

Keywords: Transfusion medicine, Acquired coagulopathies, Replacement therapies, Blood coagulation

Öz

Amaç: Taze donmuş plazma (TDP) transfüzyonu modern klinik ortamlarda yaygın olarak kullanılmaktadır. Kullanım ile ilgili uygulamalar, randomize çalışmalardaki kılavuzların eksikliğinden dolayı değişiklik gösterir. Bu çalışmanın amacı, Yunanistan'da TDP üretimi, kullanımı ve israfına ilişkin hem mevcut uygulamaları hem de kalite kontrolünün uygulanmasını, kadın donör plazma üretim politikalarını ve farmasötik hemostatik ajanların kullanımını değerlendirmektir.

Gereç ve Yöntemler: Çalışma, Şubat–Nisan 2018'de gerçekleştirildi. Çalışmanın ilk bölümü için TDP transfüzyon endikasyonu, hastane bölümü, tanı, TDP üniteleri/transfüzyon sayısı, ABO uyumluluğu, kan vericinin cinsiyeti ve dışlama nedenleri gibi veriler toplandı. İkinci bölüm için anket verileri analiz edildi.

Bulgular: Yirmi Yunan Hastanesi'nden alınan verilere göre, incelenen zaman diliminde 5069 transfüzyon sırasında 12655 TDP ünitesi 2700 hastaya nakledildi. Hastaların çoğu dahiliye, genel cerrahi ve yoğun bakım ünitelerinde yatırıldı. Her hasta ortalama 4,69 ünite (2,5 ünite/transfüzyon) aldı. Olguların %63,44'ünde transfüzyon talepleri uluslararası yönergelerle uygun olup, ünitelerin %99,04'ü ABO özdeş hastalara verilmiştir. Dışlamanın temel nedenleri arasında kalite gereksinimlerini karşılamama (%30,06), kadın donörler (%22,17) ve diğer nedenler (%27,26) yer aldı. Ülke çapındaki tüm transfüzyon hizmetlerinin %96,9'u arasında, %28,26'sı Avrupa İlaç ve Sağlık Hizmetleri Kalitesi Direktörlüğü'nün talimatlarına göre kalite kontrol gerçekleştirmekte ve %68,83'ü kadın donörlerden plazmayı dışlamaktadır. Hastanelerin %37,23'ünde farmasötik hemostatik ajanlar kullanılmaktadır.

Sonuç: Bu çalışma, Yunanistan'da TDP üretimi ve transfüzyonu ile ilgili ilk ulusal anketir. TDP ile transfüzyon yapılan hastaların çoğunun hastaneye kaldırıldığı dahiliye, genel cerrahi ve yoğun bakım ünitesi departmanlarının personeli, çağdaş transfüzyon kılavuzları konusunda düzenli olarak eğitime dahil edilmelidir. TDP üretiminin ve envanter yönetiminin yakında merkezileştirilecek olması, TDP kullanımına ilişkin uygulamaların homojenleştirilmesine ve ürün kalitesinin iyileştirilmesine yardımcı olabilir. Farmasötik hemostatik ajanların kullanımının güçlendirilmesi, hastaların yönetimini iyileştirebilir.

Anahtar Sözcükler: Transfüzyon tıbbı, Edinilmiş koagülopatiler, Yerine koyma tedavileri, Kan pıhtılaşması

Introduction

Fresh frozen plasma (FFP) is used for patients with abnormal coagulation test results due to consumption or decreased production of coagulation factors, who either bleed (therapeutic use) or undergo invasive procedures or surgery (prophylactic use). FFP transfusion is also indicated for immediate anti-vitamin K-reversal, for patients with thrombotic thrombocytopenic purpura (TTP), and for congenital coagulation factor deficiencies when alternative therapies are not available [1].

These indications are described in currently used guidelines in many countries, including Greece [2,3], but they are not supported by evidence from high-quality randomized trials

[2,3]. This fact together with the underestimation of the adverse effects of FFP use often result in a lack of strict adherence to FFP usage guidelines. Notably, the percentage of inappropriate FFP requests varies between 10% and 73% according to published data [4].

This study was conducted in order to assess and evaluate current trends in FFP production and use in Greece (request etiology, dosage/transfusion episode, cases of inappropriate use, discards). We also evaluated the implementation of FFP quality control (QC), female donor plasma production policies, and the use of pharmaceutical hemostatic agents. Having established the current status in our country, we could develop effective

educational strategies to achieve higher compliance with the international guidelines.

Materials and Methods

This study was conducted by the Working Committee of Transfusion and Apheresis of the Hellenic Society of Hematology during a 3-month period (February–April 2018) and all 97 blood transfusion services (BTSs) in Greece were invited to participate.

It consists of two parts; the first part focuses on FFP origin, use, and disposal. An electronic data collection form (Excel 2016, Microsoft Corp., Redmond, WA, USA) was used. Recorded data included i) FFP data (transfusion date, etiology, number of transfusion episodes, FFP units' ABO group, origin - male/female donor, produced in-house/imported), ii) patients' data [age, ABO group, clinical department, diagnosis, pre-transfusion international normalized ratio (INR)], and iii) data about discarded FFP units (ABO group, etiology, date of discarding). All participants were provided with a coded list of FFP transfusion indications (Table 1). The transfusion of several plasma units on the same day is defined as a "single transfusion episode." Data regarding national plasma units' supplies and usage were provided by the Hellenic National Blood Transfusion Center.

The second part of the study comprises three questions. Participating BTSs answered them by filling out the electronic data form or responded by means of a phone interview by a member of the Working Committee. The aim here was to assess i) whether QC of the produced plasma units was performed according to the requirements of the European Directorate for the Quality of Medicines & Health Care (EDQM) [5], ii) local policies regarding the production of plasma from female donors, and iii) the use of pharmaceutical hemostatic agents [prothrombin complex concentrate (PCC), fibrinogen concentrate, recombinant activated factor VII (rVIIa)].

Statistical Analysis

Electronic spreadsheet data forms (Excel 2016, Microsoft Corp., Redmond, WA, USA) and SAS software version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) were used for the statistical analysis. For all tests the significance level was set to $p < 0.05$

and the confidence interval (CI) to 95%. The results are reported as mean value and standard deviation (SD) for the arithmetic parameters and as percentages for the categorical.

Results

Data were collected from 20 of the 97 BTSs (20.62%) invited to join this study. Twelve are located in Athens and the remaining eight are located in other cities (Thessaloniki, Patras, Ioannina, Alexandroupolis, Korinthos, Rhodes, Livadia, Edessa).

A total of 12655 FFP units were transfused to 2700 patients in 5069 transfusion episodes. Given that the number of FFP units annually transfused in Greece is approximately 250000, the number of units transfused over this 3-month period is representative of the corresponding annual consumption (CI 95%, error margin 0.85%). The number of FFP units used by hospitals located in Athens was 7620 (60.2%) and the remaining 5035 (39.8%) units were used by hospitals in the rest of the country. FFP units transfused in every participating hospital, the number of patients who received FFP, the number of transfusion episodes, and the number of units/episode in each hospital are listed in Table 2.

Each patient received an average of 4.7 units (range: 1-280, SD: 12.6). The average number of episodes/patient was 1.88 ± 2.33 , while a mean number of 2.5 ± 2.61 units was used in each episode.

The majority of the units were transfused to patients admitted to internal medicine ($28.57 \pm 0.79\%$), surgery ($16.02 \pm 0.64\%$), ICU ($15.79 \pm 0.64\%$), neurological ($5.65 \pm 0.41\%$), and hematology ($3.99 \pm 0.35\%$) departments, while $9.22 \pm 0.51\%$ of the units were transfused in private hospitals (Table 3).

Patients with solid tumors ($n=429$) received the most FFP units (1780 units, $14.07 \pm 0.61\%$, 4.15 units/patient), followed by patients with sepsis ($n=241$ patients, 1101 units [$8.70 \pm 0.49\%$], 4.57 units/patient), autoimmune diseases ($n=28$ patients, $n=1020$ units [$8.06 \pm 0.48\%$], 36.43 units/patient), liver disease ($n=134$ patients, $n=817$ units [$6.46 \pm 0.43\%$], 6.1 units/patient), major gastrointestinal bleeding ($n=205$ patients, $n=668$ units

Code	Indication
FFP1	Disseminated intravascular coagulation (DIC) with co-existing clinical manifestations and laboratory findings
FFP2	Liver disease (INR ≥ 1.5 or PT ≥ 1.5 x normal rate)
FFP3	Massive bleeding (goal INR ≥ 1.5 and APTT: 46-48 s)
FFP4	Reversal of coumarin action - lack of prothrombin complex pharmaceuticals
FFP5	Thrombotic thrombocytopenic purpura (TTP)
FFP6	Preoperative transfusion of a patient with coagulopathy disorders
FFP7	Other (rationale required)

INR: International normalized ratio; PT: prothrombin time.

Table 2. Participating hospitals, respective FFP units, episodes of transfusion, and units/episode in each hospital.

Hospital	FFP units (%)	Patients (%)	Units/patient	Transfusion episodes (%)	Episodes/patient	Units/episode
HA1	1867 (14.75%)	356 (13.19%)	5.24	798 (15.74%)	2.24	2.34
HA2	1306 (10.32%)	340 (12.59%)	3.84	749 (14.78%)	2.20	1.74
HA3	1031 (8.15%)	268 (9.93%)	3.85	471 (9.29%)	1.76	2.19
HA4	783 (6.19%)	167 (6.19%)	4.69	331 (6.53%)	1.98	2.37
HA5	605 (4.78%)	153 (5.67%)	3.95	254 (5.01%)	1.66	2.38
HA6	591 (4.67%)	110 (4.07%)	5.37	207 (4.08%)	1.88	2.86
HA7	483 (3.82%)	107 (3.96%)	4.51	246 (4.85%)	2.30	1.96
HA8	359 (2.84%)	91 (3.37%)	3.95	160 (3.16%)	1.76	2.24
HA9	281 (2.22%)	94 (3.48%)	2.99	127 (2.51%)	1.35	2.21
HA10	169 (1.34%)	93 (3.44%)	1.82	113 (2.23%)	1.22	1.50
HA11	100 (0.79%)	29 (1.07%)	3.45	44 (0.87%)	1.52	2.27
HA12	45 (0.36%)	18 (0.67%)	2.50	25 (0.49%)	1.39	1.80
HOA1	1928 (15.24%)	126 (4.67%)	15.30	278 (5.48%)	2.21	6.94
HOA2	868 (6.86%)	190 (7.04%)	4.57	313 (6.17%)	1.65	2.77
HOA3	616 (4.87%)	130 (4.81%)	4.74	172 (3.39%)	1.32	3.58
HOA4	326 (2.58%)	97 (3.59%)	3.36	186 (3.67%)	1.92	1.75
HOA5	272 (2.15%)	87 (3.22%)	3.13	140 (2.76%)	1.61	1.94
HOA6	123 (0.97%)	43 (1.59%)	2.86	64 (1.26%)	1.49	1.92
HOA7	39 (0.31%)	26 (0.96%)	1.50	34 (0.67%)	1.31	1.15
HOA8	863 (6.82%)	175 (6.48%)	4.93	357 (7.04%)	2.04	2.42
TOTAL	12655 (100.00%)	2700 (100.00%)	4.69	5069 (100.00%)	1.88	2.50

HA: Hospital in Athens; HOA: Hospital outside of Athens; FFP: fresh frozen plasma; HA1: General Hospital "Laikon"; HA2: General Hospital "Tzannion"; HA3: General Hospital "Agios Panteleimon"; HA4: University Hospital "Attikon"; HA5: General Hospital "Sismanoglion"; HA6: General Hospital "Thriasion"; HA7: Oncology Hospital "O Agios Savvas"; HA8: University Hospital "Areteion"; HA9: General Hospital "Konstantopoulion"; HA10: General Hospital "Asklipiion"; HA11: General and Oncology Hospital "Oi Agioi Anargyroi"; HA12: General Hospital "Pammakaristos"; HOA1: "AHEPA" University Hospital of Thessaloniki; HOA2: University Hospital of Alexandroupolis; HOA3: University Hospital of Patras; HOA4: General Hospital of Korinthos; HOA5: General Hospital of Rhodes; HOA6: General Hospital of Pella; HOA7: General Hospital of Livadia; HOA8: University Hospital of Ioannina.

Table 3. Distribution of patients who received FFP grouped by clinical department.

Clinical department	Transfused units (%)	Patients (%)	Units/patient	Transfusion episodes (%)	Episodes/patient	Units/episode
Internal medicine	3615 (28.57%)	725 (26.85%)	4.99	1457 (28.74%)	2.01	2.48
Surgery	2075 (16.4%)	624 (23.11%)	3.32	972 (19.18%)	1.55	2.13
Intensive care unit (adults)	1998 (15.79%)	225 (8.33%)	8.88	606 (11.96%)	2.69	3.30
Private hospitals	1167 (9.22%)	299 (11.07%)	3.90	668 (13.18%)	2.23	1.75
Neurology	715 (5.65%)	17 (0.63%)	42.06	77 (1.52%)	4.53	9.29
Hematology	505 (3.99%)	63 (2.33%)	8.02	208 (4.10%)	3.30	2.43
Orthopedics	368 (2.91%)	188 (6.96%)	1.96	232 (4.58%)	1.23	1.59
Cardiac surgery	311 (2.46%)	81 (3.00%)	3.84	98 (1.93%)	1.21	3.17
Oncology	303 (2.39%)	35 (1.30%)	8.66	91 (1.80%)	2.60	3.33
Nephrology	286 (2.26%)	26 (0.96%)	11.00	55 (1.09%)	2.12	5.20
Urology	278 (2.20%)	96 (3.56%)	2.90	153 (3.02%)	1.59	1.82
Obstetrics-gynecology	145 (1.15%)	72 (2.67%)	2.01	84 (1.66%)	1.17	1.73
Vascular surgery	111 (0.88%)	34 (1.26%)	3.26	44 (0.87%)	1.29	2.52
Thoracic surgery	103 (0.81%)	34 (1.26%)	3.03	41 (0.81%)	1.21	2.51
Emergency department	87 (0.69%)	28 (1.04%)	3.11	29 (0.57%)	1.04	3.00
Neurosurgery	83 (0.66%)	30 (1.11%)	2.77	35 (0.69%)	1.17	2.37
Kidney transplantation unit	70 (0.55%)	15 (0.56%)	4.67	31 (0.61%)	2.07	2.26
Gastroenterology	63 (0.50%)	21 (0.78%)	3.00	37 (0.73%)	1.76	1.70
Cardiology	47 (0.37%)	17 (0.63%)	2.76	19 (0.37%)	1.12	2.47
Bone marrow transplantation unit	36 (0.28%)	2 (0.07%)	18.00	33 (0.65%)	16.50	1.09
Pediatrics	45 (0.36%)	9 (0.33%)	5.00	13 (0.26%)	1.44	3.46
Intensive care unit (pediatric)	26 (0.21%)	1 (0.04%)	26.00	3 (0.06%)	3.00	8.67
Pneumonology	23 (0.18%)	6 (0.22%)	3.83	8 (0.16%)	1.33	2.88

Table 3. Continued.

Clinical department	Transfused units (%)	Patients (%)	Units/patient	Transfusion episodes (%)	Episodes/patient	Units/episode
Plastic surgery	18 (0.14%)	7 (0.26%)	2.57	10 (0.20%)	1.43	1.80
ENT	12 (0.09%)	6 (0.22%)	2.00	6 (0.12%)	1.00	2.00
Other	165 (1.31%)	39 (1.45%)	4.23	59 (1.16%)	1.53	2.79
Total	12655 (100.00%)	2700 (100.00%)	4.69	5069 (100.00%)	1.88	2.50

FFP: Fresh frozen plasma.

[5.28±0.39%], 3.26 units/patient], Guillain-Barre syndrome (n=5 patients, n=430 units [3.40±0.32%], 86 units/patient), and TTP (n=3 patients, n=396 units [3.13±0.31%], 132 units/patient).

Among the predefined indications of Table 1, optimization of coagulation prior to surgery was the main indication of transfusion. FFP transfusion indications, the number of patients and units transfused, the number of transfusion episodes, the number of units/episode, and the episodes/patient are depicted in Table 4.

Coagulation screening tests were available for 3824 out of 5069 (75.44±1.19%) transfusion episodes. Among these, prolonged

prothrombin time (INR of ≥1.5) was found in 1514 episodes while the remaining had INR of <1.5. In these two categories of episodes, 3476 (27.47%) and 4970 (39.27%) FFP units were transfused, respectively. No coagulation testing was available for 1255 (24.76±1.19%) episodes in which 4209 (33.36%) of the total units were transfused.

Most patients (n=1598, 59.19±1.86%) were transfused with a total number of ≤2 FFP units, while 1102 patients (40.81±1.86%) received ≥3 units. Most of the patients who received ≤2 units had an unspecified transfusion etiology (n=419), while among

Table 4. Etiology for FFP transfusions, numbers of patients, transfusion episodes, units/patient, episodes/patient, and units/episode.

Etiology	FFP units (%)	Patients (%)	Units/patient	Transfusion episodes (%)	Episodes/patient	Units/episode
Preoperative transfusion of a patient with coagulopathy disorders (FFP6)	2530 19.99%	792 29.33%	3.19	1193 23.54%	1.51	2.12
DIC (FFP1)	1761 13.92%	307 11.37%	5.74	776 15.31%	2.53	2.27
TTP (FFP5)	1290 10.19%	17 0.63%	75.88	118 2.33%	6.94	10.93
Liver disease (FFP2)	1277 10.09%	246 9.11%	5.19	605 11.94%	2.46	2.11
Massive bleeding (FFP3)	1017 8.04%	207 7.67%	4.91	375 7.40%	1.81	2.71
Reversal of OA (FFP4)	332 2.62%	106 3.93%	3.13	149 2.94%	1.41	2.23
Other (FFP7)*	1965 15.53%	404 14.96%	4.86	771 15.21%	1.91	2.55
Not specified (FFP8)**	2483 19.62%	621 23.00%	4.00	1082 21.35%	1.74	2.29
TOTAL	12655 100.00%	2700 100.00%	4.69	5069 100.00%	1.88	2.50

DIC: Disseminated intravascular coagulopathy; TTP: thrombotic thrombocytopenic purpura; OA: oral anticoagulants.

*Other not predefined etiologies in which plasma transfusion could be characterized as "reasonable" (inappropriate but justified FFP use) are major gastrointestinal bleeding, plasmapheresis due to Guillain-Barre syndrome, hypoalbuminemia, hypofibrinogenemia, hypovolemia, intraoperative and postoperative use with or without bleeding, reversal of non-coumarin anticoagulants, use of asparaginase, thromboelastography results, burns, and premature birth.

**Missing documentation: inadequate compliance with the predefined etiologies (inappropriate and unjustified FFP use).

those who were given ≥ 3 units, preoperative FFP transfusion was the most common etiology ($n=289$) and TTP was the least common one ($n=13$).

The distribution of FFP units transfused according to ABO blood group is depicted in Table 5.

All participating BTSs in our study, with one exception, collect blood and produce blood components themselves and also import units from other hospitals whenever there is a need to cover increased demands (Table 6). Single-donor plasmapheresis is not routinely performed and plasma is almost exclusively produced from whole blood donations. The great majority

Table 5. ABO groups of FFP units and how they were used.

Patient's ABO group	FFP units' ABO groups and their percentages in the total number of units				
	A	AB	B	O	Total
A	5270 (41.64%)	36 (0.28%)	3 (0.002%)	12 (0.009%)	5321 (42.04%)
AB	3 (0.02%)	565 (4.46%)	6 (0.04%)	2 (0.01%)	576 (4.55%)
B	1 (0.008%)	31 (0.24%)	1697 (13.41%)	0 (0%)	1729 (13.66%)
O	6 (0.04%)	10 (0.08%)	7 (0.05%)	5002 (39.53%)	5025 (39.7%)
Unknown	0 (0%)	4 (0.03%)	0 (0%)	0 (0%)	4 (0.03%)
Total	5280	646	1713	5016	12655

Identical transfusions are marked in shaded cells. Incompatible transfusions are marked in bold.

Almost all plasma units ($n=12651$, $99.97\pm 0.04\%$) were given to patients of known ABO groups. Compatible plasma was given in 12628 of 12655 cases ($99.78\pm 0.09\%$). In 12534 ($99.25\pm 0.18\%$) of them, the plasma was identical to the patient's ABO group, while in 27 cases ($0.22\pm 0.17\%$) the plasma was incompatible with the patient's ABO group, and 14 of these units were of O group and were given to non-O patients.

Table 6. FFP units produced in house vs. imported FFP units.

Hospital	FFP				
	Produced FFP	Imported FFP	Not stated	Total FFP	% FFP
HA1	1823	44	0	1867	14.75%
HA2	918	358	30	1306	10.32%
HA3	834	197	0	1031	8.15%
HA4	732	51	0	783	6.19%
HA5	605	0	0	605	4.78%
HA6	402	189	0	591	4.67%
HA7	441	42	0	483	3.82%
HA8	359	0	0	359	2.84%
HA9	281	0	0	281	2.22%
HA10	169	0	0	169	1.34%
HA11	94	6	0	100	0.79%
HA12	0	45	0	45	0.36%
HOA1	1172	756	0	1928	15.24%
HOA2	781	87	0	868	6.86%
HOA3	527	89	0	616	4.87%
HOA4	326	0	0	326	2.58%
HOA5	171	101	0	272	2.15%
HOA6	110	13	0	123	0.97%
HOA7	39	0	0	39	0.31%
HOA8	698	165	0	863	6.82%
TOTAL	10482	2143	30	12655	100%

HA: Hospital in Athens; HOA: Hospital outside of Athens; FFP: fresh frozen plasma; HA1: General Hospital "Laikon"; HA2: General Hospital "Tzannion"; HA3: General Hospital "Agios Panteleimon"; HA4: University Hospital "Attikon"; HA5: General Hospital "Sismanogliou"; HA6: General Hospital "Thriasion"; HA7: Oncology Hospital "O Agios Savvas"; HA8: University Hospital "Areteion"; HA9: General Hospital "Konstantopoulou"; HA10: General Hospital "Asklipeion"; HA11: General and Oncology Hospital "Oi Agioi Anargyroi"; HA12: General Hospital "Pammakaristos"; HOA1: "AHEPA" University Hospital of Thessaloniki; HOA2: University Hospital of Alexandroupolis; HOA3: University Hospital of Patras; HOA4: General Hospital of Korinthos; HOA5: General Hospital of Rhodes; HOA6: General Hospital of Pella; HOA7: General Hospital of Livadia; HOA8: University Hospital of Ioannina.

of units (n=10537, 83.26±0.65%) were donated by males; 1042 (8.23±0.48%) were donated by females, while for the remaining 1076 (8.5±0.49%), the donor's sex was not stated.

As for the discarding of the plasma produced, 5538 units were disposed of. Almost half of them (2738 units (49.44±1.32%)) were meant to be destroyed by the time of venipuncture and the rest at a later stage of the procedure (Table 7).

In the second part of the study, 94 out of the total of 97 BTSs (96.9±3.82%) in Greece answered our questions. Regarding the QC of the produced plasma, 26 of the 92 BTSs (28.26±9.06%) to answer this question perform it following the directions of the EDQM [5]. The remaining 66 BTSs (71.74±9.06%) partly follow the above-mentioned directions, mostly due to the unavailability of the necessary medical technology (e.g., analyzers for measuring FVIII levels).

With respect to how plasma from female donors is handled, our study revealed that 60 BTSs (63.83±9.54%) discard plasma from female donors, 27 (28.72±9.00%) produce plasma from female donors with ≤2 pregnancies, 5 (5.32±4.78%) produce plasma with no differentiation between male and female donors, and 2 (2.13±3.42%) do not produce plasma at all.

Concerning the use of hemostatic agents, 35 BTSs (37.23±9.59%) use such medicines, while the remaining 49 (52.13±9.59%) do not. Four BTSs (4.25±4.39%) use other methods to achieve hemostasis (e.g., cryoprecipitate) and 6 (6.38±5.14%) did not answer.

Discussion

This study represents the first attempt to present the current practice regarding FFP production and use in Greece, depicting the status before the launching of the central inventory

management system that the Hellenic National Blood Transfusion Center has already started. Centralization in the blood supply chain is a well-established practice in developed countries worldwide [6,7]. Notably, decentralization in blood collection and the preparation and distribution of blood components leads to a variety of practices affecting many procedures along the blood transfusion chain [8,9].

The distribution of patients grouped by clinical department in Greece (Table 3) does not seem to differ from distributions in other countries (e.g., England), as in other studies most patients were hospitalized in internal medicine, surgical wards, and ICUs [1].

It is worth noting that plasma transfusion trends and policies vary worldwide. In several countries (e.g., UK, Canada, Iran), increased or improper FFP use has been reported. This is in line with our results that revealed a significant level of inappropriate use of this blood component. The lack of strong evidence supporting specific plasma transfusion practices could be a possible explanation [1,10,11,12,13].

In our study, the majority of FFP units (64.85%) were given according to the predefined indications depicted in Table 1, which is in line with the percentages of other studies, ranging from 31.5% to 85% [1,14,15,16,17]. The transfusion of the 15.53% of FFP units that were not compliant with predefined indications (FFP7 category) concerned cases of emergency patients, whose transfusions were mainly based on clinical criteria (e.g., perioperative bleeding, major gastrointestinal bleeding), or patients with hypofibrinogenemia or hypoalbuminemia in hospitals where neither human albumin nor fibrinogen concentrates or cryoprecipitate were available. Similarly, several studies outlined surgery-related conditions (even with mild or no elevated laboratory coagulation tests),

Table 7. Reasons for plasma to be discarded.
<p>A. Meant for disposal by the time of venipuncture: 2738 units (49.44%)</p> <ul style="list-style-type: none"> • Female donor: 1228 (22.17%) • Other causes (e.g., duration of collection, men with a history of transfusion, information given during collection): 1510 (27.26%)
<p>B. Not meant for disposal by the time of the venipuncture: 2800 units (50.56%)</p> <p>B1. Prior to inclusion in the inventory</p> <ul style="list-style-type: none"> • Positive infection markers screening and/or confirmatory testing: 197 (3.55%) • Failure to meet requirements (underweight, abnormal color): 1665 (30.06%) <p>B2. Included in the inventory</p> <ul style="list-style-type: none"> • Return of thawed plasma that was not finally transfused: 383 (6.91%) • Post-donation information (PDI): 83 (1.5%) • Expiration of use-by-date: 54 (0.9%) • Used as samples for quality control: 20 (0.36%) • DAT-positive (detected because of an incompatible crossmatch): 8 (0.14%) <p>B3. Not specified (regardless of inclusion in the inventory)</p> <ul style="list-style-type: none"> • Leakage/breakage: 211 (3.81%) • Other causes: 179 (3.23%)

hypoalbuminemia, and burns as the most common reasons for FFP use outside of strict indications [14,16,17]. Apart from this inappropriate but justified FFP use, the transfusion of 19.62% of plasma units remained unjustified (FFP8 category), which underlines the need for more consistent documentation of FFP requests by clinicians and the need for reevaluation of FFP requests, possibly by the BTS staff. Implementation of continuous and repeated education regarding FFP transfusion indications and use of electronic clinical decision support systems could help in reducing inappropriate FFP requests [18].

Regarding the FFP doses in our study, our observation of FFP underuse is consistent with what is reported in the international literature [19]. Given that the indicated FFP dose is 10-15 mL/kg, our data show that patients receive less than the recommended volume (2.5 units/episode), with exceptions for patients who undergo plasma exchange and receive the indicated dose.

ABO-identical plasma was given in the vast majority of cases, and only a few ABO-incompatible plasma units (27/12655) were transfused. According to the Hellenic Hemovigilance Center's annual reports, no case of hemolytic transfusion reaction due to FFP transfusion was recorded from 2012 to 2018 [20,21], which is consistent with data reporting that even when plasma concentrates of "dangerous" universal O blood group donors are given to a non-O patient, the actual incidence of hemolytic transfusion reactions is low [22,23]. Additionally, no significant differences have been found regarding complications and mortality between patients transfused with ABO-compatible and ABO-incompatible plasma [24].

Regarding wastage (Table 7), the most common reasons for discarding units in our study was return from the clinical wards, leakage, and breakage, as previously described. The wastage rate due to expiry date was quite low (0.9%), while in other studies it was higher [12,25,26]. Although wastage underreporting could not be ruled out, this finding may reflect a proper inventory management according to the "first in, first out" (FIFO) policy [27,28].

As for the use of female-origin plasma and plasma-containing components, it has been reported that it has been implicated in the pathogenesis of the majority of transfusion-related acute lung injury (TRALI) fatalities [29]. Several strategies have been implemented in many countries to reduce the risk of TRALI related to female donor deferral, but these are not yet standardized and they differ between individual blood banks [30,31]. Our study also reveals this variety, which is linked to decentralization and reflects not only the lack of concrete national recommendations but also the efforts of some BTSs to ensure an adequate inventory. This practice may be connected

to data from the 2018 annual report of the Hellenic National Hemovigilance Center, which shows two FFP-related TRALI cases and one TRALI-related death in 2018 [21]. Nevertheless, we cannot confirm that those cases took place within the 3-month period of our study.

Regarding plasma QC, many countries follow the World Health Organization's recommendation for performing QC under the spectrum of a centralized model of blood collection and preparation of blood components [32]. This model could provide uniform quality of all blood derivatives and could also relieve local BTSs from a considerable laboratory and economic burden [33]. In Europe, many countries have already implemented centralized QC policies according to the EDQM directives [5,34]. In our country, less than one-third of the BTSs follow these directives, which can be attributed to the decentralized management of preparation of blood components and the lack of the necessary medical technology, especially in the smaller BTSs.

Pharmaceutic hemostatic agents such as fibrinogen concentrate and PCC have been widely incorporated into current therapeutic algorithms for the treatment of massive hemorrhage in trauma patients, intraoperatively, and in cases of obstetric hemorrhage [35,36]. Their use is widespread in many countries and numerous studies have demonstrated their clinical benefits over FFP [37,38,39]. The low rate of use of hemostatic agents recorded in our study may not reflect the true picture, since the provision of these agents may not be carried out exclusively through BTSs. Nevertheless, strengthening the use of pharmaceutic hemostatic agents could improve patients' management in our country.

Conclusion

This is the first national study regarding FFP use in Greece. Internal medicine and surgery departments as well as ICUs are the major FFP consumers; thus, their personnel could be the first to be trained in guidelines for proper FFP use. The reasons for FFP requests include not only situations included in the national guidelines but also other situations that, according to these guidelines, are not considered to be indications for FFP transfusion. Various practices regarding plasma production have been noticed; almost every hospital has its own blood establishment and most of the transfused units are produced in-house. FFP is mainly produced from male donors. The main reasons for discarding FFP are not meeting the quality requirements and the returning of thawed plasma that was not finally transfused. Pharmaceutic hemostatic agents are not widely used in all Greek hospitals. Centralization in the production and distribution of blood components could help in ensuring uniformity in all practices and better inventory management.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: A.A.; Design: A.A., S.V., E.G.; Data Collection or Processing: A.P., A.A., S.V., M.G., A.Ag., V.V., V.P., T.A., A.P., C.A., V.G., P.S., S.T., G.M., E.K., E.Z., S.K., E.Ky., A.M., D.L., A.C., A.T., M.B., I.A., D.M., A.L., M.P., F.R., C.P., V.K., N.V., A.G., I.D., F.S., L.L., Z.A., V.S., K.M., A.S., G.K., K.L., K.S., E.G.; Analysis or Interpretation: A.P., A.A., S.V., E.G.; Literature Search: A.A., S.V., E.G.; Writing: A.A., S.V., E.G.

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