

Glimpse on Hemostatic Changes Produced By Plasmapheresis

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Abstract

Background: The basic idea of aphaeresis is efficient removal of a circulating blood component, either cells (Cytopheresis) or plasma solute (plasmapheresis, plasma exchange). Thus, the treatment goal of aphaeresis is to remove the circulating cell or substance directly responsible for the disease process by automated cell separators in that ensure selectively removal of one or more of blood components from the blood and return the remainder to the individual. Plasmapheresis is separation of plasma from blood cells which are returned to the body. It is accompanied by changes in many haemostatic parameters were found when two different replacement fluids were used.

Objective: To determine the effect of:

1. Therapeutic Plasma Exchange (TPE) on selected parameters of hemostasis with each Replacement fluid used and comparing between the effects of the two solutions.
2. Total volume of Plasma Exchanged (PE), spacing between sessions and number of sessions on coagulation screening tests.

Patients and Methods: This clinico-haematological study was conducted during a period of six months, from February 2004 to July 2004 at the National Blood Transfusion Center / Baghdad & 50 patients underwent Therapeutic Plasma Exchange for various disorders for 3-12 sessions with two different replacement fluids were used & two types of automated blood cell separators (Haemonetics MCS plus & Fresenius AS.TEC 204) were applied. Venous blood samples were collected immediately before & after the first session & after the last

session. Control group of 20 persons were included in this study.

Results: The changes in Prothrombin Time, Partial Thromboplastin Time, Thrombin Time, Fibrinogen, Platelets count, Haemoglobin and Packed Cell Volume were significant after TPE. There was no significant difference in changes in crystalloid group from that in Fresh Frozen Plasma (FFP) group. In crystalloid group, significant correlation was observed between Prothrombin Time, Activated Partial Thromboplastin Time, Thrombin Time & volume of PE /session, while spacing between sessions and the number of sessions was significantly correlated with Thrombin Time. Plasma fibrinogen concentration and platelets count were decreased in the patients included in this study.

Conclusion: There is no significant difference in changes in haemostatic system whether crystalloid or diluted FFP was used as replacement fluid. Thus, crystalloid, solution devoid from coagulation material can be used as a replacement fluid in the TPE if the volume of PE is small which will minimize the usage of blood components as a safer replacement fluid substitute.

Key words: fresh frozen plasma, therapeutic plasma exchange.

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Introduction

The primary objective of aphaeresis is efficient removal of a

circulating blood component, either cell, (Cytopheresis) or plasma solute (plasmapheresis, plasma exchange). For most disorders, the treatment goal is to remove the circulating cell or substance directly responsible for the disease process ^(1, 2) (antibodies, immune complexes, abnormal RBCs, malignant WBCs, platelets, protein-bound drugs or toxins). ⁽³⁾ Current

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automated aphaeresis instrument use microprocessor technology to administer an anticoagulant, collect the treated blood, separate component either by centrifugation or by filtration, isolate the desired component or recombine the remaining component for return to the patient or donor ⁽²⁾. Therapeutic Plasma Exchange (TPE) is generally associated with rapid (and repeated) removal of large quantities of plasma and its associated coagulant proteins ^(1, 4, 5, 6). When coagulant protein-deficient replacement fluid such as albumin, saline, or colloidal starch are used, an acute fall in clotting factor activity, varying from 40% to 70% of baseline, can be observed immediately after exchange. This depletion is usually associated with a small prolongation in measured prothrombin time (PT) and activated partial thromboplastin time (PTT)^(1,5,6). The total amount of PE, spacing in days between sessions and number of sessions in the full course of exchange are the three factors directly related to the procedure of plasmapheresis & are expected to affect the outcome of procedure especially the part related to derangement of coagulation parameters ⁽¹⁹⁾.

Patients and Methods

From February 2004 to July 2004, a total of 50 patients underwent Therapeutic Plasma Exchange (TPE) for various disorders referred to National Center for Blood Transfusion during this study period were included. The study groups included 22 females and 28 males, with age range from 6 years to 64 years. Those patients include the followings: (10) Myasthenia Gravis; (25) Guillian Barre Syndrome (GBS) ; (5) Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) ; (1) Pemphigus; (1) Renal failure for transplantation ; (1) Thrombotic Thrombocytopenic Purpura (TTP) ;

(1) Multiple Sclerosis (MS) & (6) Rh-immunized pregnant . Two types of automated blood cell separators (Haemonetics MCS + which represent an intermittent flow centrifugation technique – IFC & Fresenius AS. TEC 204 which represent the continuous flow centrifugation technique - CFC) were used in this study. No instrument specific effects on coagulation screening tests were detected in this study.

A course of Therapeutic Plasma Exchange (TPE) includes 3 to 12 sessions at 1 to 11 days interval. About 1000 ml of plasma was exchanged each session. A 9% Normal saline used as a replacement fluid for 25 patients and FFP was used for remainder (i.e. other 25 patients). Blood samples were collected from the patients before and immediately after 1st session and immediately after the last session. PT, PTT, TT, fibrinogen, platelets, Hb and PCV performed immediately.

The control group of consist of 20 age & sex matched individuals, for whom screening tests (Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Thrombin Time (TT), Fibrinogen (FNG), Platelets count, Haemoglobin (Hb) and Packed Cell Volume (PCV) had been performed.

Sampling:

Patient Group:

Blood samples were collected from the patients before and immediately after the first session and immediately after the last session. A 5 ml of venous blood was collected by clean venepuncture in two collecting tubes, 1.8 ml dispensed in plain plastic tube containing 0.2 ml of 0.11μ aqueous trisodium citrate dehydrate for coagulation study. The remaining blood was dispensed in 2.5 ml ethylenediamine tetra-acetic acid (EDTA) containing tube with

concentrate of 1.5 mg EDTA per one ml of blood for determination of platelet count, Hb, PCV and antibody titration. The citrated blood was centrifuged at 2000 g for 15 minutes to get platelet poor plasma (PPP), the later was used for performing Prothrombin time(PT), Activated Partial Thromboplastin time(APTT), Thrombin time(TT) and fibrinogen level(FNG). All the tests performed at Quality Control laboratory in National Blood Transfusion Center - Iraq.

Control Group:

This study includes a control group of 20, age and sex matched healthy individuals. Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Thrombin Time (TT), Fibrinogen (FNG) had been performed.

Haematological screening tests:

All haematological screening tests were done on the study group include

Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Thrombin Time (TT), Fibrinogen (FNG), Platelets count, Haemoglobin (Hb) and Packed Cell Volume (PCV) according to the standard technical procedures recommended by the manufacture & consistent with the international references of practical hematology⁽²²⁾. All coagulation studies were performed immediately after blood collection.

Statistical analysis

Data were translated into a computerized database structure. Statistical analyses were compute assisted using SPSS ver. 10 (Statistical Package for Social Sciences).

Frequency distribution for selected variables was done first. For variables that were assumed to be normally distributed the statistical significance of mean change observed after plasmapheresis was assessed by Paired t-test, while for a non-normally distributed variable like Antibody titer

Wilcoxon signed rank test was used. The statistical significance of difference in mean between the 2 groups was assessed by Independent samples t-test. The statistical significance of association between 2 categorical variables in a small sample size was assessed Fisher's exact test. P value less than the 0.05 level of significance was considered statistically significant.

Multiple regression models was used to study the independent and net effect of the total amount of plasma exchange, number and spacing between plasmapheresis sessions on the response variable, which is the change in coagulation parameters after the last session compared to baseline.

Result

According to the type of fluid used to replace the exchanged plasma subtracted by plasmapheresis in this study, our patients were divided into two grouped: First group (Crystalloid group): 25 patients were included & for whom the volume of the plasma subtracted by plasmapheresis was substituted by crystalloid while the second group (FFP group): 25 patients were included & for whom the Fresh Frozen Plasma (FFP) was used to substitute the volume of plasma subtracted by plasmapheresis had been utilized.

The frequency distribution of the study sample by reported reason for plasmapheresis, age, sex & the type of replacement fluid used were tabulated (See table 1 & table 2)

Table 1: Frequency distribution of the study sample with different diagnoses for plasmapheresis in crystalloid & FFP groups.

Diagnosis (reason for plasmapheresis)	Crystalloids group		FFP group	
	No.	%	No.	%
Guillian Barre Syndrome	12	48	13	52
Myasthenia Gravis	3	12	7	28
Chronic Renal Failure	0	0	1	4
TTP	0	0	1	4
Pemphigus	0	0	1	4
Polyneuropathy	3	12	2	8
Multiple sclerosis	1	4	0	0
Isoimmunization	6	24	0	0
Total	25	100	25	100

Table 2: Frequency distribution of the study sample for plasmapheresis by age and sex in crystalloid & FFP groups.

Age in years	Crystalloids group		FFP group	
	No.	%	No.	%
Children (<15)	3	12	0	0
Young Adults (15-49)	17	68	20	80
Older adults (50+)	5	20	5	20
Gender				
Female	15	60	7	28
Male	10	40	18	72
Total	25	100	25	100

In this study , patients within the crystalloid group having abnormally prolonged PT, PTT, TT after a course of TPE were as in the followings: 12(60%), 6(25%), 1(4%) respectively,

versus 11(50%) of patients showing abnormally prolonged PT with no change in PTT & TT in FFP group(See table 3)

Table 3: Abnormal prolonged coagulation times with a baseline normal value for PT, PTT & TT parameters after the first and last session of plasmapheresis in crystalloid & FFP groups.

Subjects with normal parameter	Crystalloids group					FFP group				
	Total	Abnormally prolonged after the first session		Abnormally prolonged after the last session		Total	Abnormally prolonged after the first session		Abnormally prolonged after the last session	
	No.	No.	%	No.	%	No.	No.	%	No.	%
PT	20	11	55	12	60	22	9	40.9	11	50
PTT	24	1	4.2	6	25	25	0	0	0	0
TT	25	2	8	1	4	25	0	0	0	0

On the other hand, patients within the crystalloid group of this study having abnormally low value of fibrinogen, platelets count, Hb and PCV were as in the followings:

2(8%), 2(9.5%), 3(21.4) and

3(15.8) respectively versus 1(4%), 4(17.4%), 4(19%) and 7(31.8%) patients respectively in FFP group as it listed in Table 4.

Table 4: Abnormal low value for Fibrinogen, Platelet count, Hb & PCV selected parameters after the first and last session of plasmapheresis in crystalloid & FFP groups.

Crystalloids group						FFP group				
Subjects With normal parameter	Total	Abnormally low after the first session		Abnormally low after the last session		Total	Abnormally low after the first session		Abnormally low after last session	
	No.	No.	%	No.	%	No.	No.	%	No.	%
Fibrinogen	25	0	0	2	8	25	0	0	1	4
Platelet count	21	2	9.5	2	9.5	23	0	0	4	17.4
Hb	14	0	0	3	21.4	21	1	4.8	4	19
PCV	19	1	5.3	3	15.8	22	1	4.5	7	31.8

The changes in the all selective parameter (PT, PTT, TT, fibrinogen, platelets count, Hb and PCV) are significant after TPE in crystalloid group with a P value of ≤ 0.001 but they are minimal and many values remain with normal range. There is no significant difference in the changes in crystalloid from that in FFP group.

The underlying reasons for the inability to test all the parameters for all the groups members included in this study was due to many reasons mainly due to insufficient preliminary blood samples, needs for additional blood samples for repetition of tests due to technical errors & others with impossibility to recall the patients within the proper time limits because of poor compliance of the patients &

the real difficulties because of the current situation of the country.

In crystalloid group there is significant correlation between total amount of plasma exchanged in the full course of PE and PT, PTT, TT with a P value 0.004, 0.008 and <0.001 respectively. There is significant correlation between spacing between sessions in days and number of sessions with TT only with a P value 0.04 and 0.01 respectively. In FFP group all the three factors (total amount of PE, spacing between sessions and number of sessions) had no significant correlation with the coagulation screening tests. No bleeding or thrombotic sequel reported in this study. (See table 5).

Table 5: The range and mean or median of selected variables by type of replacement fluid used.

Total amount of plasma exchange (ml) in the full course of exchanges	Crystalloids group		FFP group Immune diseases
	(Rhesus iso- immunization)	(others)Autoimmune disease	
Range	(3020 - 6050)	(628 - 5128)	(2420 - 13764)
Mean	4953.3	2746.8	4316.7
SE	542	293	459
Mean amount of plasma exchanged per session (ml)			
Range	(500 - 560)	(188 - 1026)	(600 - 1966)
Mean	512.3	602.6	849.4
SE	10	57	54
Duration of the full course of exchanges(days)			
Range	(30 - 112)	(5 - 11)	(4 - 30)
Median	82	7	7
Spacing between sessions in days			
Range	(5 - 11)	(1 - 3)	(1 - 3)
Median	7	2	1
Number of sessions in the full course of exchange			
Range	(6 - 12)	(3 - 7)	(4 - 12)
Median	11	5	5

Coagulation screening tests

Control group:

A 20 age and sex matched control group were selected as volunteers. Their PT ranged between 12-14 seconds, PTT ranged between 30-40 second, the TT ranged between (13-21 sec.) while fibrinogen ranged between (1.5-4.0 g/L). These represented a normal values of the control group to which the study groups were compared statistical calculation whether significant or not.

Study group:

The changes in the PT after plasmapheresis after first and last session are shown in Table 6.

Table 6: The change in PT after plasmapheresis after the first (acute change) and last session (chronic change) in crystalloid & FFP groups.

PT (seconds)	Baseline	After the first session	Acute change	After the last session	Change after the last session compared to	
					First session	(Chronic change) - baseline
Crystalloid group						
Range	(11 to 16)	(12 to 17)	(0 to 4)	(12 to 18)	(-2 to 3)	(-1 to 6)
Mean	13.4	14.9	1.5	15.3	0.4	1.9
SE	0.25	0.27	0.2	0.35	0.3	0.39
*P (Paired t-test)			<0.001		0.22 ^[NS]	<0.001
FFP group						
Range	(12 to 16)	(13 to 18)	(0 to 3)	(13 to 17)	(-2 to 2)	(0 to 3)
Mean	13.3	14.8	1.4	14.6	-0.1	1.3
SE	0.21	0.28	0.14	0.25	0.2	0.17
*P (Paired t-test)			<0.001		0.56 ^[NS]	<0.001
**P (Student's t-test)=	0.72 ^[NS]		0.81 ^[NS]		0.18 ^[NS]	0.2 ^[NS]

* Paired t-test for the statistical significance of mean change after plasmapheresis.

**Independent samples t-test for the statistical significance of difference in mean between the 2 groups.

In both crystalloid group and FFP group the mean of acute change was increased by 1.5s versus 1.4s, while the mean of chronic change was 1.9s versus 1.3s, these changes are statistically significant [$P < 0.001$] however they are clinically not significant.

The mean of acute & chronic changes in PT in the crystalloid group was not significant from that of FFP group with P value = 0.81, 0.2 respectively

The mean of acute change and chronic change in PTT in the crystalloid group was not significant

from that of FFP group with P value = 0.07, 0.09 respectively. In crystalloid group the relative frequency of subject in whom the PTT increased by more than 7s after last session compared to baseline was 5 (20%) (3 patients PTT increased by 8s, 1 patient by 9s and 1 patient by 10s). Patients who received FFP as replacement fluid show no significant increase in the PTT. The change in PTT after plasmapheresis after first (acute change) and last session (chronic change) in both crystalloid group and FFP group are shown in Table 7.

Table 7: Change in PTT after plasmapheresis after the first (acute change) & last session (chronic change).

PTT (seconds)	Baseline	After the first session	Acute change	After the last session	Change after the last session compared to	
					First session	(Chronic change) baseline
Crystalloids group						
Range	(30 to 41)	(33 to 42)	(-1 to 4)	(31 to 45)	(- 4 to 7)	(-4 to 10)
Mean	34.2	36.2	2	37.6	1.4	3.4
SE	0.59	0.5	0.27	0.71	0.61	0.74
*P (Paired t-test)			<0.001		0.031	<0.001
FFP group						
Range	(32 to 37)	(33 to 40)	(0 to 3)	(34 to 39)	(-1 to 2)	(0 to 3)
Mean	34.2	35.6	1.4	35.8	0.2	1.6
SE	0.29	0.33	0.21	0.23	0.19	0.15
*P (Paired t-test)			<0.001		0.31 ^{NS}	<0.001
**P (Student's t-test)=	0.95 ^{NS}		0.07 ^{NS}		0.07 ^{NS}	0.09 ^{NS}

* Paired t-test for the statistical significance of mean change after plasmapheresis.

**Independent samples t-test for the statistical significance of difference in mean between the 2 groups

In both crystalloid and FFP group the mean of acute change was increased by 2s versus 1.4s, while the mean of chronic change was 3.4s versus 1.6s, these changes are statistically significant with a P value

of <0.001 however they are clinically not significant.

The change in TT after plasmapheresis after first (acute change) and last session (chronic change) in both crystalloid group and FFP group are shown in Table 8.

Table 8: The change in TT after TPE after the first (acute change) and last session (chronic change).

TT (seconds)	Baseline	After the first session	Acute change	After the last session	Change after the last session compared to	
					First session	baseline
Crystalloids group						
Range	(11 to 21)	(13 to 22)	(0 to 4)	(12 to 22)	(-3 to 5)	(-3 to 8)
Mean	15	16.4	1.5	17.6	1.1	2.6
SE	0.54	0.53	0.17	0.5	0.49	0.57
*P (Paired t-test)			<0.001		0.032	<0.001
FFP group						
Range	(11 to 18)	(12 to 20)	(0 to 3)	(13 to 21)	(-1 to 4)	(0 to 6)
Mean	13.4	14.8	1.4	15.6	0.8	2.2
SE	0.28	0.33	0.15	0.48	0.28	0.33
*P (Paired t-test)			<0.001		0.008	<0.001
**P (Student's t-test)=	0.012		0.86 ^{NS}		0.57 ^{NS}	0.59 ^{NS}

* Paired t-test for the statistical significance of mean change after plasmapheresis.

**Independent samples t-test for the statistical significance of difference in mean between the 2 groups.

In both crystalloid and FFP groups the mean of acute change was increased by 1.5s versus 1.4s, while the mean of chronic change was 2.6s versus 2.2s, these changes are statistically significant with P value<0.001 however they are clinically not significant. The mean of acute and chronic changes in TT in the crystalloid group was not significant from that of FFP group with P value =0.86 and 0.59 respectively.

In crystalloid group the relative frequency of subject in whom the TT

increased by more than 5s after last session compared to baseline was 5 (20%) patients (2 patients TT increased by 6s, 2 by 7s and 1 patient by 8s), while in FFP group 2 patients increased more than 5s (2 patients increased by 6s). Table 3-12

The change in fibrinogen after plasmapheresis after first (acute change) and last session (chronic change) in both crystalloid group and FFP group are shown in Table 9.

Table 9: Change in fibrinogen concentration after TPE after the first (acute change) and last session (chronic change).

Fibrinogen conc. (gm/L)	Baseline	After the first session	Acute change	After the last session	Change after the last session compared to	
					First session	Baseline
Crystalloid group						
Range	(1.9 to 3.7)	(1.8 to 3.3)	(-0.7to -0.1)	(1.4 to 2.8)	(-1.1to -0.1)	(-1.7 to -0.2)
Mean	3	2.6	-0.4	2.1	-0.5	-0.9
SE	0.09	0.08	0.03	0.07	0.05	0.07
*P (Paired t-test)			<0.001		<0.001	<0.001
FFP group						
Range	(1.9 to 3.7)	(1.6 to 3.4)	(-0.6 to 0.7)	(1.4 to 3.1)	(-1.9 to -0.1)	(-2.1 to 0)
Mean	2.9	2.7	-0.2	2.2	-0.5	-0.7
SE	0.11	0.09	0.06	0.08	0.08	0.09
*P (Paired t-test)			<0.001		<0.001	<0.001
**P (Student's t-test)=	0.82 ^[NS]		0.1 ^[NS]		0.94 ^[NS]	0.36 ^[NS]

* Paired t-test for the statistical significance of mean change after plasmapheresis.

**Independent samples t-test for the statistical significance of difference in mean between the 2 groups

In both crystalloid and FFP group the mean of acute change was reduced by 0.4gm/l versus 0.2gm/l respectively while the mean of chronic change was reduced by -0.9 versus -0.7, these changes are statistically significant with P value<0.001 however they are clinically not significant. The mean of acute and chronic change in fibrinogen

in the crystalloid group was not significant from that of FFP with P valve of 0.1 and 0.36 respectively.

The change in platelets count after plasmapheresis after first (acute change) and last session (chronic change) are shown in Table 10.

Table10: Change in Platelets count after TPE after the first (acute change) & last session (chronic change).

Platelets count (X1,000,000,000/L)	Baseline	After the first session	Acute change	After the last session	Change after the last session compared to	
					First session	Baseline
Crystalloid group						
Range	(121 to 477)	(113 to 440)	(-97 to -7)	(103 to 401)	(-134 to -3)	(-159 to -11)
Mean	295	263.9	-31.1	220.6	-43.3	-74.4
SE	17.18	15.3	4.34	14.04	5.65	6.67
*P (Paired t-test)			<0.001		<0.001	<0.001
FFP group						
Range	(132 to 403)	(120 to 388)	(-87 to -8)	(106 to 310)	(-150 to -13)	(-209 to -26)
Mean	284.8	252.5	-32.4	202.8	-49.7	-82
SE	13.76	11.94	3.96	10.07	7.19	9
*P (Paired t-test)			<0.001		<0.001	<0.001
**P (Student's t-test)=	0.65 ^[NS]		0.83 ^[NS]		0.49 ^[NS]	0.5 ^[NS]

* Paired t-test for the statistical significance of mean change after plasmapheresis.

**Independent samples t-test for the statistical significance of difference in mean between the 2 groups

In both crystalloid and FFP group the mean of acute change was reduction by $-31.1 \times 10^9/L$ versus $-32.4 \times 10^9/L$, while the mean of chronic change was a reduction by $-74.4 \times 10^9/L$ versus $-82 \times 10^9/L$, these changes are statistically significant with a P value <0.001 however they are clinically not significant. The mean of acute and

chronic change in platelet count in the crystalloids group was not significant from that of FFP with a P value of 0.85 and 0.5 respectively.

The change in Hb concentration after plasmapheresis after first (acute change) and last session (chronic change) are shown in Table 11.

Table 11: Change in blood Hb concentration after TPE after the first (acute change) & last session (chronic change).

Blood Hb conc. (gm/L)	Baseline	After the first session	Acute change	After the last session	Change after the last session compared to	
					First session	Baseline
Crystalloid group						
Range	(104 to 154)	(103 to 155)	(-3 to 3)	(94 to 151)	(-27 to 1)	(-27 to 1)
Mean	127.1	126.8	-1.8	122.7	-4.1	-4.4
SE	3.38	3.32	0.26	3.68	1.26	1.21

*P (Paired t-test)			0.003		0.003	0.001
FFP group						
Range	(71 to 157)	(68 to 157)	(-11 to 4)	(65 to 154)	(-7 to 1)	(-15 to 4)
Mean	133.6	132.2	-1.5	129.7	-2.5	-4
SE	3.76	3.93	0.49	3.99	0.42	0.72
*P (Paired t-test)			0.006		<0.001	<0.001
**P (Student's t-test)=	0.2 ^[NS]		0.35 ^(N S)		0.22 ^[NS]	0.76 ^[NS]

* Paired t-test for the statistical significance of mean change after plasmapheresis.

**Independent samples t-test for the statistical significance of difference in mean between the 2 groups

In both crystalloid and FFP groups the mean of acute change was reduction by -0.3gm/L versus -1.5gm/L while the mean of chronic change was reduction by - 4.4gm/L versus -4gm/L, these changes are statistically significant with a P value<0.001 however they are clinically not significant.

The mean of acute and chronic change in Hb concentration in the crystalloid group was not significant from that of FFP with P value of 0.35 and 0.76 respectively.

The change in PCV after plasmapheresis after first (acute change) and last session (chronic change) are shown in Table 12.

Table 12: The change in PCV after plasmapheresis after the first (acute change) and last session (chronic change).

					Change after the last session compared to	
PCV L/ L	Baseline	After the first session	Acute change	After the last session	First session	Baseline
Crystalloid group						
Range	(0.33 to 0.55)	(0.32 to 0.52)	(-0.03 to 0.04)	(0.28 to 0.48)	(-0.1 to 0.02)	(-0.13 to 0.01)
Mean	0.404	0.4	-0.004	0.38	-0.019	-0.023
SE	0.0113	0.0118	0.0034	0.0105	0.0056	0.0062
*P (Paired t-test)			0.25 ^[NS]		0.002	0.001
FFP group						
Range	(0.22 to 0.55)	(0.2 to 0.55)	(-0.06 to 0.02)	(0.18 to 0.5)	(-0.05 to 0.01)	(-0.09 to -0.01)
Mean	0.429	0.416	-0.014	0.392	-0.024	-0.037
SE	0.013	0.0137	0.0033	0.0131	0.0032	0.0036
*P (Paired t-test)			<0.001		<0.001	<0.001
**P (Student's t-test)=	0.14 ^[NS]		0.9 ^(N S)		0.5 ^[NS]	0.06 ^[NS]

* Paired t-test for the statistical significance of mean change after plasmapheresis.

**Independent samples t-test for the statistical significance of difference in mean between the 2 groups

In both crystalloid and FFP group the mean of acute change was reduction by -0.004L/L versus -0.014L/L while the mean of chronic changes was reduction by -0.023L/L versus -0.037L/L, these changes are statistically significant with P value ≤ 0.001 however they are clinically not significant (except acute change in crystalloid group which is statistically and clinically not significant). The mean of acute and chronic change in PCV in the crystalloid group was not significant from that of FFP with P value of 0.9 and 0.06 respectively.

Discussion

In this study, small volume plasmapheresis (about 500 – 1000 ml / session) was selected instead of a more extensive procedure (i.e. the volume of plasma to be exchanged is more than 1000 ml / session) because this involves minimal risks for patients. A 25 patients received fluids devoid from coagulation protein ((0.9 % Normal Saline(NS)) as in other studies ⁽⁴⁻¹²⁾ and the other 25 patients received diluted FFP (FFP/NS 1:1) as in many studies ⁽¹³⁻¹⁷⁾ TPE is generally associated with rapid and repeated removal of large quantities of plasma and its associated coagulant protein. When replacement fluid which is deficient in coagulation protein is used a fall in clotting factors activities can be observed immediately after the exchange. ^(1, 18) In this study, depletion of coagulation proteins was observed as a slight prolongation in PT, PTT, TT

The prolongation in coagulation screening tests in crystalloid group (e.g. Rh- isoimmunization) was higher but not significant from that in FFP. These minimal changes in coagulation screening tests are most likely due to small volume of PE which is the usual practice at the national blood transfusion center.

In this study, the range of exchanged plasma volume per a session of TPE in Rh isoimmunization – crystalloid group - is from 500 to 560 ml). These findings agree with Mark E. Brecher study ⁽¹⁾ as the prolongation is slight in the measured PT, PTT and TT, although such values frequently remain within normal range. The total amount of PE, spacing in days between sessions and number of sessions in the full course of exchange are the three factors directly related to the procedure of plasmapheresis & are expected to affect the outcome of procedure especially the part related to derangement of coagulation parameters ⁽¹⁹⁾. In crystalloid group, significant correlation was found between total amount of PE in the full course of plasmapheresis and the coagulation screening tests. These findings are mostly due to increase loss of coagulant proteins with increasing total amount of PE, while spacing between sessions in days and number of sessions show significant correlation with TT only.

These findings could be due to the direct relation between TT and fibrinogen level ⁽⁶⁾. In FFP group, all the three factors (total amount of plasma exchange, spacing between session and number of sessions) have no significant effect on coagulation screening tests (PT, PTT and TT) because there is partial replacement of coagulation material ^(20, 21). In this study, it has been found that there is a significant reduction in fibrinogen level in the crystalloid and FFP group. This has been demonstrated by the study of Domen et al ⁽⁶⁾, Flum et al ⁽⁹⁾ and Chrinside et al ⁽¹¹⁾ as they demonstrated that fibrinogen was efficiently depleted by plasma exchange and its removal was maximal, where as less efficient removal was seen for other factors. In this study, the consequence of PE is a reduction in

circulating platelet but with no significant difference between crystalloid and FFP. This is consistent with the finding of Bracher et al⁽¹⁾ and Strobel⁽³⁾.

The current study shows a minimal reduction in PCV/Hb after a course of PE and this could be due to using of developed machines, small volume PE & replacement fluid. The vascular access was obtained from large veins, the free flow of blood from obstruction, the adequately needle bore diameter & the use of FFP & isotonic solution (0.9 % Normal Saline) as a replacement solution. All these measures diminished the risk of hemolysis & dilution. This is consistent with the findings of Foke et al⁽²³⁾ & Susan et al⁽²⁴⁾.

In addition to that, no hemorrhage was observed during or after PE in the patients of this study even after repeated plasmapheresis at short intervals.

It was concluded that Crystalloid, solution devoid from coagulation material can be used as a replacement fluid in the TPE if the volume of PE is small; in crystalloid group, significant correlation was observed between PT, PTT, TT and volume of PE/session, while spacing between sessions and the number of sessions was significantly correlated with TT.

Plasma fibrinogen concentration and platelets count were decreased acutely & over the period of the study, however it was clinically not significant.

There was a minimal reduction in PCV/Hb after a course of PE.

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