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PREVALENCE OF COMPLICATIONS OF THERAPEUTIC PLASMA EXCHANGE IN ICU PATIENTS

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Abstract: Background: Plasma exchange (PE) is a procedure in which the plasma is separated from the blood, discarded in total, and replaced with a substitution fluid such as albumin or with donated plasma from a healthy person. This also is generally performed to remove toxins or autoantibodies that have accumulated in the plasma.

Aim of the study: To evaluate the prevalence of complications of therapeutic plasma exchange and assess the safety of its use.

Patients and method: it is a prospective study that was conducted in ICU by anesthesia and intensive care department of Al-Diwanyah teaching hospital \ Iraq. During the period between January 2021 and november 2022 , a total number of 96 sessions done for 31 patients admitted for plasmapheresis , these patients were monitored subjectively, objectively and by blood tests for complications ,pre-per-and post each session .

Results: most complications reported during sessions in this study were non-life-threatening and patients completed their sessions with proper or no intervention at all, these included paresthesia in 5%, muscle cramps in 1%, CVL complications in 2.1%, anemia in 58.3%, hypotension in 7.3%, hypothermia in 26%, tachycardia in 10.4%, fever in 6.3%, leukopenia in 8.4%, thrombocytopenia in 11.5%, hypoalbuminemia in 31.3%, hypocalcemia in 29.2% and hypokalemia in 36.5% .

Life-threatening complications included hemolysis 1% and anaphylaxis 1% and no mortality.

Conclusion: with proper patient monitoring, therapeutic plasma exchange can be considered a safe procedure.

Key words: Therapeutic plasma exchange, complications.

Introduction:

Apheresis is an extracorporeal medical technology in which the blood of a patient is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation. Leukapheresis or lymphocytapheresis also describes apheresis procedures in which the white blood cells are isolated and retained. As another example, peripheral stem cell collection, done in preparation for autologous bone marrow transplant, involves an apheresis procedure in which the critical stem cells are isolated and retained.

Plasmapheresis is generally performed to remove and discard harmful substances (e.g., toxins or autoantibodies), which have accumulated in the plasma. It is hypothesized that removal of these factors can be therapeutic in certain situations[(1)]. Plasmapheresis is a term used to refer to a broad range of procedures

in which extracorporeal separation of blood components results in a filtered plasma product [2]. The filtering of plasma from whole blood can be accomplished via centrifugation or the use of semipermeable membranes [3]. Plasma exchange (PE) is a procedure in which the plasma is separated from the blood, discarded in total, and replaced with a substitution fluid such as albumin or with donated plasma from a healthy person. This also is generally performed to remove toxins or autoantibodies that have accumulated in the plasma [1].

The principal mechanism of action consists of removing circulating autoantibodies, immune complexes, cytokines, monoclonal proteins, toxins and other inflammatory mediators [4]. Therapeutic plasma exchange is an extracorporeal blood purification technique designed for the removal of large-molecular weight substances. Examples of these substances include pathogenic auto-antibodies, immune complexes, cryoglobulins, myeloma light chains, endotoxin, and cholesterol-containing lipoproteins. For TPE to be a rational choice as a blood purification technique, at least 1 of the following conditions should be met:

1) The substance to be removed is sufficiently large (15,000 dalton) to make other less expensive purification techniques unacceptably inefficient (ie, hemofiltration or high-flux dialysis).
2) The substance to be removed has a comparatively prolonged half-life so that extracorporeal removal provides a therapeutically useful period of diminished serum concentration.
3) The substance to be removed is acutely toxic and resistant to conventional therapy so that the rapidity of extracorporeal removal is clinically indicated [5].

The separation and removal of plasma from the patient by a semipermeable membrane and its simultaneous replacement by an equal volume of appropriate fluid purify the blood by removing the pathogenic molecules responsible for certain diseases. The substances removed by plasma exchange are abnormally produced in the body in various diseased states. These high molecular weight pathogenic molecules, such as Igs, proteins, or immune complexes cannot be removed from the blood by conventional methods, such as dialysis or hemo-filtration, due to their large size. Urgent removal of these molecules is necessary to prevent ongoing organ damage because these molecules have long half-lives; additionally, therapies aimed at suppression of their production take weeks or months to be effective. Rapid removal of these large molecules by plasma exchange reduces morbidity and mortality. The commonly removed molecules and their molecular weights are:

Separation of plasma from the blood's cellular components can be accomplished by filtration through a highly permeable membrane. This methodology separates the blood into its cellular and noncellular components by subjecting it to sieving through a membrane with pores that allow the plasma proteins to pass but retain the larger cellular elements within the blood path, twenty-five years after the first centrifugal plasma exchange procedure in a patient with multiple myeloma in 1952, the membrane separation technique was introduced in 1978as an alternative to the existing centrifugal technique. Membrane separation plasma exchange is very similar to the operation of a conventional dialysis machine running in ultrafiltration mode or a continuous RRT (CRRT) in venovenous hemofiltration mode. In membrane separation plasma exchange, instead of a regular filter designed for the removal of small and "middle" molecules, a special filter with large pores (0.3–0.5 *M*m) is used. Pore sizes of these membranes are usually 0.5Mm or less, thus easily rejecting the smallest cellular component, the platelets (3 Mm). Blood drawn from a central venous access, such as a dialysis catheter, is passed through this special plasma filter before it is returned to the patient. Because of the large pores, the ultrafiltrate or effluent produced in this manner contains all of the non-cellular components of the patient's plasma ; as plasma is filtered out, it is replaced simultaneously with appropriate fluids (usually albumin or fresh frozen plasma [FFP]) in equal volume to the plasma removed to prevent hemodynamic compromise .The removal rate of any given plasma component depends on the plasma filtration rate and its sieving coefficient (ratio of a given plasma protein or solute concentration between the filtrate and the blood side of the membrane). With the currently

available modern plasma filtration membranes, the sieving coefficient of even the largest molecules, weighing more than 1 million D (LDL cholesterol, etc.), is essentially "one." Thus, the concentration of these larger proteins in the removed plasma (effluent) is essentially equal to that in the patient's circulating plasma[8,9].

Patients and methods:

Setting and analysis

During the period between January 2021 and november 2022 a prospective study was conducted in ICU in Al-Diwanyah Teaching Hospital by the department of anesthesia and intensive care unit, where 96 sessions of plasmapheresis are accomplished for 31 patients in an average of 3-5sessions for each patient, time of sessions ranged from (2-4)hours .

Inclusion criteria:

1. ASA Class I .
2. Category I according to ASFA(The Apheresis Application Committee of the American Society for Apheresis) which include : (disorders for which apheresis accepted as first line therapy either as primary standalone treatment or in conjunction with other modes of treatment).

Exclusion criteria:

No exclusion criteria apart from mentioned age limitation and ASA classification.

The following where done for all patients before and after sessions:

1. History and physical examination.

2.Complete blood picture.

3. Serum electrolyte and arterial blood gas analysis.

4. Coagulation profile including : PT,PTT,INR ,Fibrinogen levels.

5. Total Serum bilirubin.

6.Total serum proteins and serum albumin.

7. Vascular access was femoral central venous line inserted under aseptic technique .

During the sessions the patient were continuously monitored for vital signs (including temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation), signs and symptoms of hypocalcemia including parasthesia and numbness, muscle cramps, patients also had been monitored for dyspnea, palpitation, chest pain, itching, skin rash, change in consciousness level and any other new onset complaints.

Replacement fluid :

The type and amount of supplementary fluids depended on the patients clinical condition and were based on monitoring of cardiovascular functions, water-electrolyte and acid--base balance. The volume of replacement fluid had been the same as that of the effluent obtained. In adults, the effluent had been replaced with crystalloid solutions only if the volume extracted is less than 1000 ml. When a larger volume is extracted, colloids had been used, with 4-5% human albumin being the colloid of choice. For this purpose, 20% human albumin is diluted with crystalloids or polyelectrolyte solutions. Patients received on average 1000-1500 ml crystalloids (either 0.9% normal saline or ringer lactate), 400 mL of 20% albumin solution, 3–4 units of fresh frozen plasma (FFP), 5 mL of 10% calcium gluconate for each unit of transfused plasma were administered. The procedures were planned in such a manner as to transfuse the amount of fluid equal to the volume of plasma removed and tailored to the patient clinical condition.

Anticoagulation : patient were given unfractionated heparin as a single bolus of 3000 -5000 IU , followed by 1000 IU / hour as needed with continuous monitoring of activated clotting time.

the patient's plasma volume is estimated on the basis of the hematocrit and weight of the patient in kilograms. A formula to estimate plasma volume is (0.065 × weight [kilograms]) × (1- hematocrit). Plasma exchanged volume is usually prescribed as 1–1.5 ×estimated plasma volume. The rate of blood flow depended on the circulatory efficiency and was maintained within the limits of 50–60 mL/minute Transmembrane pressure was within 20–70 mm Hg.

Data were reported as the following :

Subjective: symptoms reported by the patient.

Objective: signs observed during the sessions, procedure related complications and change in laboratory values compared to reference range and central line related complications.

The possible complications were defined as:

A fall in arterial blood pressure was defined as a drop in baseline value by over 20%. Abnormal heart rate was determined according to the WHO definitions(The normal pulse for healthy adults ranges from **60 to 100 beats per minute**). Fever was defined as an increase in body temperature above 38 C at normal baseline value. Hypothermia is body temperature below 35C . The abnormalities in laboratory tests included: anemia (hemoglobin concentration < 14 g/ dL for male and < 12 g /dL for female patients), leukocytopenia (WBC < 4 000 cell/dl), thrombocytopenia (PTC < 150000 /dl), hypokalaemia (serum potassium level < 3.5 mmol /dl), hyponatraemia (serum sodium level < 135 mmol/dl), and hypocalcaemia (serum calcium level < 2.1 mmol/ dl).

Data Analysis: Statistical analysis was carried out using SPSS version 27. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Pearson chi-square test and Fisher's exact test were used to find the association between categorical variables. A *p*-value of ≤ 0.05 was considered as significant.

Results:

Figure 3.1 shows distribution of patients according to age (years) including (< 20 years, 20-30 years, 30-40 years and ≥ 40 years). Majority of patients (N=43, 44.8%) presented with age (20-30) years, (N=29, 30.2%) of patients presented with age of (30-40) years, (N=18, 18.8%) of patients presented with age (≥ 40 years) and only six patients (6.3%) of patients presented with age (< 20 years). Mean age of patients was (30.56 ± 9.89) years with maximum age was (56.00) years and minimum age was (16.00) years.

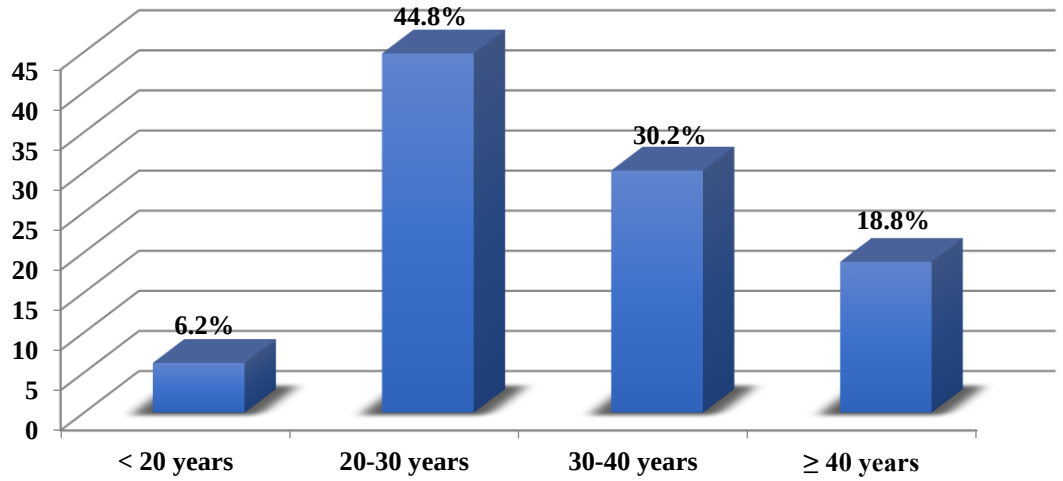


Figure 3.1 : Distribution of patients according to age (N=96)

Figure 3.2 shows distribution of patients according to gender including (male and female). Majority of patients (N=84, 87.5%) were female, while only (N=12, 12.5%) of patients were males.

Figure 3.3 shows distribution of patients according to diagnosis including (Gullian barre syndrome, Myasthenia gravis and Thrombotic thrombocytopenic purpura). Majority of patients (N=70, 72.9%) presented with Gullian barre syndrome. Myasthenia gravis represent (N=22, 22.9%) of patients and Thrombotic thrombocytopenic purpura represent four patients (4.2%) of patients.

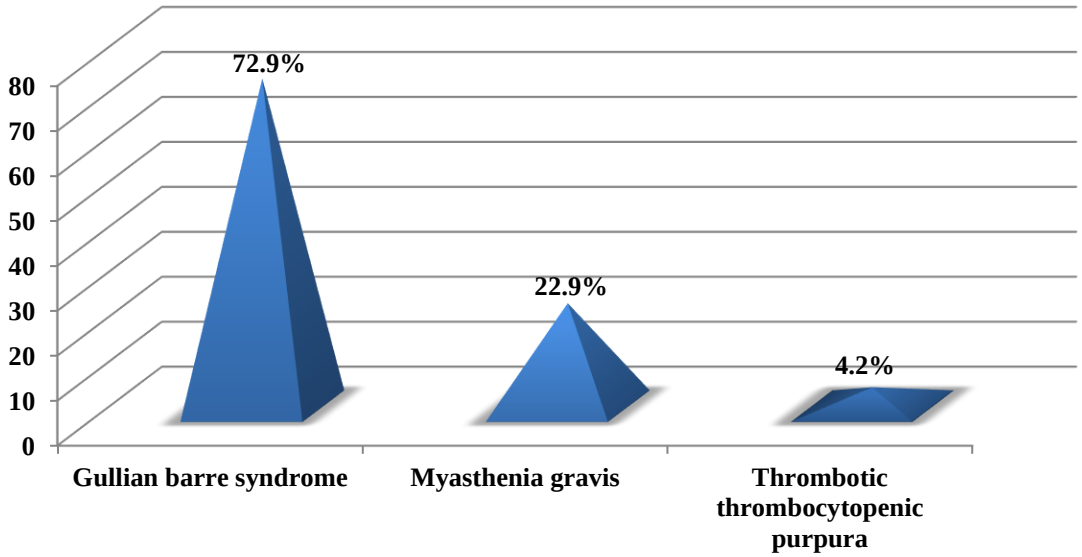


Figure 3.3: Distribution of patients according to diagnosis (N=96)

Table 3.1: The Distribution of patients according complications (N=96).

Complications	Number of patients	Percentage %
Paresthesia and numbness	5	5.2%
Central venous line complications	2	2.1%
Anaphylaxis	1	1.0%
Muscle cramps	1	1.0%
Hemolysis	1	1.0%
Anemia (<10 mg/dl)	56	58.3%
Leukopnea (WBC < 4000 Cell/microliter)	8	8.4%
Leukocytosis (WBC >12000 Cell /microliter)	3	3.2%
Thrombocytopnea (< 150000 cell/microliter)	11	11.5%
Tachycardia (>100 bpm)	10	10.4%
Hypotension (BP ≤ 90/60)	7	7.3%
Hypothermia (< 36 Celsius)	25	26%
Fever (>37.5 Celsius)	6	6.3%
Hypoalbuminemia (< 4 mg /dl)	30	31.3%
Hypochloremia (< 98 meq/dl)	10	10.4%
Hyponatremia (< 135 meq/dl)	21	21.9%
Hypocalcemia (< 8.5 meq/dl)	28	29.2%
Hypokalemia (< 3.5 meq/dl)	35	36.5%

Table 3.1 shows distribution of patients according to complications including (Parasthesia and numbness, Central venous line complications, Anaphylaxis, Muscle cramps, Hemolysis, Anemia, Leukopenia or Leukocytosis, Thrombocytopnea, Hypoalbuminemia, Tachycardia, Hypotension, Hypothermia or Fever, Hypochloremia, Hyponatremia, Hypocalcemia and Hypokalemia).

Table 3.2: Mean ± SD and range of vital signs and hematological parameters of study patients (N=96)

Parameters		(Mean ± SD)	Range
Vital signs	Heart rate (bpm)	(91.42 ± 13.04)	(77-150)
	Systolic blood pressure (mmHg)	(113.43±11.58)	(80-150)
	Diastolic blood pressure (mmHg)	(75.83 ± 7.06)	(60-90)
	Mean blood pressure	(87.45±8.4)	(70-110)
	Respiratory rate	(16 ± 2)	(12-20) cycle/minute
	Temperature (Celsius)	(36.34 ± 1.44)	(34-40)
	Oxygen saturation	(97±1.2)	(96-100%)
Blood parameters	Hemoglobin (mg/dl)	(10.08 ± 2.61)	(6.7-15.0)
	WBC count (Cell/microliter)	(8916.0 ± 2965.5)	(2500-14000)
	Platelets (Cell/microliter)	(182.24 ± 44.57)	(60-300)
	Serum albumin (mg /dl)	(4.21 ± 1.04)	(2.2-5.0)
Serum electrolytes	Serum potassium (meq/dl)	(3.58 ± 0.64)	(2.0-4.3)
	Serum sodium (meq/dl)	(137.23 ± 4.72)	(128.0-145.0)
	Serum calcium (mmol/dl)	(8.86 ± 1.08)	(6.5-10.5)
	Serum chloride (meq/dl)	(101.73 ± 4.69)	(88.0-106.0)

Table 3.3 Association between complications and age of patients (N=96)

Complications	Age of patients (years)				P-value
	<20	20-30	30-40	≥ 40	
Paresthesia and numbness					0.103
Positive	1 (16.7)	4 (9.3)	0 (0.0)	0 (0.0)	
Negative	5 (83.3)	39 (90.7)	29 (29.0)	18 (18.0)	
Total	6 (100.0)	43 (100.0)	29 (100.0)	18 (100.0)	
CVL complications					0.727
Positive	0 (0.0)	2 (4.7)	0 (0.0)	0 (0.0)	
Negative	6 (100.0)	41 (95.3)	29 (29.0)	18 (18.0)	
Total	6 (100.0)	43 (100.0)	29 (100.0)	18 (100.0)	
Anaphylaxis					1.000
Positive	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	
Negative	6 (100.0)	42 (97.7)	29 (29.0)	18 (18.0)	
Total	6 (100.0)	43 (100.0)	29 (100.0)	18 (100.0)	
Muscle cramps					1.000
Positive	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	
Negative	6 (100.0)	42 (97.7)	29 (29.0)	18 (18.0)	
Total	6 (100.0)	43 (100.0)	29 (100.0)	18 (100.0)	
Hemolysis					1.000
Positive	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	

Negative Total	6 (100.0) 6 (100.0)	42 (97.7) 43 (100.0)	29 (29.0) 29 (100.0)	18 (18.0) 18 (100.0)	
Anemia (<10 mg/dl) Positive Negative Total	 2 (33.3) 4 (66.7) 6 (100.0)	 24 (55.8) 19 (44.2) 43 (100.0)	 19 (65.5) 10 (34.5) 29 (100.0)	 11 (61.1) 7 (38.9) 18 (100.0)	0.505
WBC count (cell/microliter) Leukopenia (WBC < 4000) Leukocytosis (> 12000) Normal (4000-12000) Total	 1 (16.7) 0 (0.0) 5 (83.3) 6 (100.0)	 0 (0.0) 2 (4.7) 41 (95.3) 43 (100.0)	 2 (6.9) 0 (0.0) 27 (93.1) 29 (100.0)	 5 (27.8) 1 (5.6) 12 (66.6) 18 (100.0)	0.005*
Thrombocytopnea (< 150000 cell/microliter) Positive Negative Total	 1 (16.7) 5 (83.3) 6 (100.0)	 7 (16.3) 36 (83.7) 43 (100.0)	 3 (10.3) 26 (89.7) 29 (100.0)	 0 (0.0) 18 (18.0) 18 (100.0)	0.25
Tachycardia Positive Negative Total	 5 (83.3) 1 (16.7) 6 (100.0)	 4 (9.3) 39 (90.7) 43 (100.0)	 1 (3.4) 28 (96.6) 29 (100.0)	 0 (0.0) 18 (18.0) 18 (100.0)	<0.001*
Hypotension (BP ≤ 90/60) Positive Negative Total	 2 (33.3) 4 (66.7) 6 (100.0)	 4 (9.3) 39 (90.7) 43 (100.0)	 1 (3.4) 28 (96.6) 29 (100.0)	 0 (0.0) 18 (18.0) 18 (100.0)	0.065
Temperature Hypothermia (< 36 Celsius) Fever (>37.5 Celsius) Normal temperature (36.5-37.2 Celsius) Total	 4 (66.7) 0 (0.0) 2 (33.3) 6 (100.0)	 11 (25.6) 6 (14.0) 26 (60.5) 43 (100.0)	 1 (3.4) 0 (0.0) 28 (96.6) 29 (100.0)	 9 (50.0) 0 (0.0) 9 (50.0) 18 (100.0)	<0.001*
Hypoalbuminemia (< 4 mg /dl) Positive Negative Total	 0 (0.0) 6 (100.0) 6 (100.0)	 19 (44.2) 24 (55.8) 43 (100.0)	 7 (24.1) 22 (75.9) 29 (100.0)	 4 (22.2) 14 (77.8) 18 (100.0)	0.068
Hypochloremia (< 98 meq/dl) Positive Negative Total	 2 (33.3) 4 (66.7) 6 (100.0)	 5 (11.6) 38 (88.4) 43 (100.0)	 3 (10.3) 26 (89.7) 29 (100.0)	 0 (0.0) 18 (18.0) 18 (100.0)	0.12
Hyponatremia (< 135 meq/dl) Positive Negative Total	 2 (33.3) 4 (66.7) 6 (100.0)	 9 (20.9) 34 (79.1) 43 (100.0)	 8 (27.6) 21 (72.4) 29 (100.0)	 2 (11.1) 16 (88.9) 18 (100.0)	0.466
Hypocalcemia (< 8.5 meq/dl) Positive Negative Total	 2 (33.3) 4 (66.7) 6 (100.0)	 15 (34.9) 28 (65.1) 43 (100.0)	 7 (24.1) 22 (75.9) 29 (100.0)	 4 (22.2) 14 (77.8) 18 (100.0)	0.694
Hypokalemia (< 3.5 meq/dl)					0.013*

Positive	2 (33.3)	20 (46.5)	4 (13.8)	9 (50.0)	
Negative	4 (66.7)	23 (53.5)	25 (86.2)	9 (50.0)	
Total	6 (100.0)	43 (100.0)	29 (100.0)	18 (100.0)	

*P value ≤ 0.05 was significant.

Table 3.3 shows the association between complications and age of patients (years). There was significant association between age and WBC count, tachycardia, body temperature and hypokalemia)**:**

Patients with age group older than or equal to 40 years are more likely to develop leukopenia :

5 patients (27.8%) out of 18 developed leukopenia (significant p-value 0.005) during sessions.

Tachycardia is more likely to develop in patients age group younger than 20 years (5 out of 6 patients), (83.3%) of this age group developed tachycardia during sessions with significant (p-value < 0.001).

This study suggest that patients younger than 20 years and patients older than 40 years are at greater risk for hypothermia during sessions compared to other age groups, in patients age < 20 years 4 patients out of 6 (66.7%) and in age group >40 years 9 patients out of 18 (50%) developed hypothermia during sessions Significant (p-value < 0.001).

Our study suggest that age group older than 40 years are at greater risk for hypokalemia during plasma exchange : 9 patients out of 18 (50%) developed hypokalemia with a significant (p-value 0.013).

Discussion:

Plasma exchange (PE) : is a procedure in which the plasma is separated from the blood, discarded in total, and replaced with a substitution fluid such as albumin or with donated plasma from a healthy person. This also is generally performed to remove toxins or autoantibodies that have accumulated in the plasma **(10).**

This study is a prospective study that was conducted in ICU to investigate the safety and complications of therapeutic plasma exchange. It included 31 patients for them total 96 sessions of plasma exchange has been done.

This study shows that plasma exchange can be considered a safe procedure that is well tolerated , the most common complications are mild and require no intervention or moderate (require intervention but plasma exchange can be completed), life threatening complications developed in two patients (anaphylactic reaction to FFP) in 1 patient (1%) and necessitated medical treatment and procedure to be aborted but the patient recovered well, this finding is consistent with a study published by Malchesky PS et al. and Basic-Jukic N et al. which reported anaphylaxis in (0.3-0.7)% of patients**(11-14)** .

In risky patients who needs large volume replacement with FFP like those with **thrombotic** thrombocytopenic purpura anaphylaxis may be ameliorated by giving the patient 50 mg diphenhydramine intravenous pretreatment**(15).**

Other life threatening complication included hemolysis which occurred in 1patient (1%) during the session the patient developed oozing from CVL site and dark color urine and work up revealed elevated serum levels of unconjugated bilirubin and LDH and urinalysis showed hemoglobinurea, session stopped and patient given 2 liters of 0.9% N\S followed by 200 ml of mannitol and followed up closely in the ICU for next 24 hours, eventually patient recovered well and discharged to the ordinary ward .

This event may be attributed to the high transmembrane pressure (higher than 50 mmhg pressure) a plateau is reached in the filtration of the plasma and the increase in pressure across the membrane is not accompanied by an increase in the transfer of masses, increasing the risk of hemolysis**(16-18)** or it is may be related to FFP used as replacement fluid in these patients.

No death has been reported in this study while a study of Sutton DM et al. had reported mortality rate of 0.05% [19].

All other encountered complications whether clinically or biochemically were nonlife-threatening and procedures of plasma exchange had been completed in those patients with no squeal .

CVL complications in 2 patients (2.1%) one patient developed clotting and unsalvageable blockage of CVL necessitating replacement of new line on opposite site, other one patient developed puncture site hematoma that resolved spontaneously this is consistent with a study done by M J WU et al which reported CVL events in 1.5% of patients catheter infection (0.3%), catheter oozing (1.2%)[20] .

Paresthesia and numbness developed in 5 patients (5.2%) which is slightly different from a study published by Nikolina Basic-Jukic,Petar et al. which revealed paresthesia in (2.7%) of patients[21].

Muscle cramps developed in 1 patient (1%) in our study while an incidence of 36.1% of paresthesias and/or cramps was reported by Gafoor *et al*. in a study on 230 patients undergoing plasmapheresis with neurological disorders[22] these differences can be attributed to the difference of data size .

Anemia was the most common complication in this study in 56 patients (58.3%) a finding that is slightly different from a study published by Wojciech Szczeklik et al. which showed anemia in (74%) of patients[23].

Thrombocytopenea developed in 11 patients (11.5%) while a study published Wojciech Szczeklik et al. showed a higher incidence (59.26%) of thrombocytopenea [24].

Leukopenea developed in 8 patients (8.4%) this finding is slightly different from the afore mentioned study of wojciech et al**.** which reported leukopenia in (12.96%) of cases[25].

Leukocytosis reported in 3 patients in this study (3.1%) this is not attributed to plasma exchange procedure itself but is due to catheter line exit site infections which is been femoral catheter placed under completely aseptic technique, other cause which may precipitated higher risk of infection is the use of 5% albumin as the main replacement fluid in this study which is associated with a 60% depletion in blood levels of immunoglobulines and even higher depletion if repeated sessions over a short period of time[15].

Hypoalbuminemia encountered in 30 patients in our study (31.3%) detected by blood tests, these patients have had lowest normal levels of albumin before undergoing procedures and developed decreased levels on repeated sessions of plasma exchange albumin was given as replacement fluid to minimize sequel of this event.

Hypocalcemia developed in 28 patients (29.2%) in our study which is slightly higher than the korean study published by son EY et al. which reported hypocalcemia in (11.1%) of procedures[24], other study by nikolina basic et al. have reported even a lower incidence of hypocalcemia (9%) of plasma exchange procedures [25] .

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