Outcome of Therapeutic Plasma Exchange; One Year Single Center Experience

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Abstract

Background: Plasma exchange is a therapeutic procedure used to treat a wide variety of diseases through the bulk removal of plasma. Whereas the mechanism of action has been thought to be the removal of pathologic IgS, there is evidence suggesting an immune-modulatory effect. The objectives of this study were to assess the outcome of therapeutic plasma exchange in treating of several immunological and non-immunological diseases and evaluate the effectiveness of plasma exchange in management of different diseases. **Methods:** This is a descriptive study, carried out in a one year including patients who were treated using TPE; clinical data, number of sessions, volume of plasma exchanged, outcomes and complications were recorded and statistically analyzed. **Results:** Mean age of the studied cases at presentation was 9.43±3.6 with range of (3-14) years and mean weight was 35.5±12.1 with range of (12-58) kg. 36.1% of cases had GBS, 25% of cases had NS, 25% of cases had HUS, 5.6% of cases had SLE and 8.3% of cases had Amyloidosis. the mean TLC, mean HB, mean Platelets, mean urea, mean Creatinine, mean calcium, mean C3 and mean Fibrinogen findings of the studied cases. 75% of cases showed improvement after therapy, 16.7% didn't improve and 8.3% died. Number of sessions is <5 in 19.4% of cases, 5-10 in of 66.7% of cases and >10 in 13.9% of cases. Percent of haemorhage was 8.3% and percent of hypotension was 100% of cases. there is high significant relation between number of sessions and outcome. There is high significant relation between the disease and outcome. There is significant relation between complications and number of sessions. There is significant change of urea level, Hg, creatinine and platelets while there is no significant change in other lab findings. There is NO significant relation between complications and type of replacement fluid. **Conclusion:** PE can be safely performed in children. It seems that indication for PE and the presence of underlying diseases are affecting the mortality rate. Therapeutic plasma exchange is safe and effective adjuvant treatment for several diseases especially autoimmune diseases with less complications events. PE is a safe treatment method for critically ill children with the appropriate indication, and that the treatment is more effective in patients without comorbidity in addition to PE indication. The analysis of all cases of plasmapheresis in our department showed that the procedure is safe, with only minimal procedure related complications and no mortality.

Key words: Therapeutic Plasma Exchange - Outcome

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Introduction:

The terms Total plasma exchange (TPE) and plasmapheresis are used interchangeably, although the two procedures are different. Plasmapheresis removes a small amount of plasma, usually less than 15 % of the patient's blood volume, and therefore does not require replacement of removed plasma. During therapeutic plasma exchange (TPE) the whole blood is removed from patient and pass through an extracorporeal medical device, which separates the plasma from the cellular component of the blood. The plasma is removed and replaced with colloid solution (e.g. albumin and-or donated plasma) or a combination of crystalloid and colloid solution [1].

Through removal and replacement of plasma, many pathological substances such as pathological antibodies, immune complexes and cytokines are eliminated. It has been presumed that the removal of these substances represents the major mechanism of action of TPE. However, this mechanism does not explain the length of response seen in some disorders. In addition evidence

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was found that TPE may have immunomodulatory effect beyond the removal of immunoglobulins [(2).]

Therapeutic plasma exchange has been successfully used in various pediatric immunologically and non immunological mediated diseases in the last few decades. There has been profound advancement in the technique with advances in transfusion medicine.The outcomes of plasmapharesis as a therapeutic modality reported in pediatric nephrology literature are mainly based on case reports in individual diseases [(3).]

The objectives of this study were to assess the outcome of therapeutic plasma exchange in treating of several immunological and non-immunological diseases and evaluate the effectiveness of plasma exchange in management of different diseases.

Patients and Methods

(1): Technical design:

- **setting:**

  This study will be performed in nephrology unit, pediatric department, Zagazig University Hospitals, Egypt.

- **population:**

  A total of 36 children patient admitted to our nephrology unit during the study period were included to this study.

- **criteria:**

-Inclusion criteria:-

Patients will be enrolled in during the study if they are

- residients at zagazig university hospitals.
- All patients in who therapeutic plasma exchange will indicated to improve the course of disease and their quality of life will included in the study.
- Patients underlying the following resident diseases (GBS), (SLE), (MG), (HUS), (TTP).

- Exclusion criteria:

- Patients who cannot tolerate central line treatment.
- Patients who have allergies to fresh frozen plasma or albumin depending on the type of plasma exchange.
- Patients who are actively septic or are hemodynamically unstable.
- Patients with heparin allergies should not receive heparin as an anticoagulant during plasmapharesis.
- Patients outside zagazig university hospitals.

- **study design:**

Prospective cohort study.

- **-Sampling** :

  Sample size was determined by community department at zagazig medical faculty.

Assuming that rate of admission of patients undergoing plasma exchange in 3cases /month, so a comprehensive sample of 36cases will be included during a year of study.

(2) Operational design:

- **Process:**

All patients will be subjected to the following:

- Full history taking and written consents from parents to begin the study.
- Full clinical examination.
- Full laboratory Investigations as CBC, KFT,CRP , PTT , PT , Serum Albumen , Fibrinogen

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level , ABG , LFT, Clotting function test, electrolyte level ,Urine analysis , Urine culture ,Blood culture,

- Special investigation admitted to assess improvement and outcome of TPE as in …
  - ✓ Systemic lupus erythromatosis as ANA , Anti DNA , C3 , C4 , HBV , HCV , HIV , ANCA ,
  - ✓ Gillian Barrie syndrome as Nerve conduction velocity , CT MRI, fibrinogen level, Electromyography study EMG.
  - ✓ Hemolytic uremic syndrome as C3 , LDH , Blood culture , Stool analysis , Stool culture ,
  - ✓ Thrombiotic Thrombocytopenic Purpura as platelets counts, LDL level.

The outcome measures coded, entered, and analyzed using statistical analysis.

❖ *Withdrawal criteria:*

Any patient develop side effects or complications during the study.

- ➢ Time line:

  Doing the beast to perform each process activity in least time as we can with maximum one year as the total time.
- ➢ Obstacles and limitation of study:
  - Number of patients insufficient …….>overcomed by determining adequate sample size.
  - Missed cases as they want to terminate study or not completing it…..>try to discuss the reasons with parents and explain benefit of study.

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- Problems in machine used for plasma exchange due to defect in system or device…..>overcome by specific handling manner to solve the problem.

(3)Administrative design:

Approval will be taken from the Zagazig University institutional review board (IRB).

Statistical Analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage , quantitative continues group represent by mean ± SD , the following tests were used to test differences for significance;. difference and association of qualitative variable by Chi square test (X^2) . Differences between quantitative independent groups by t test or Mann Whitney, paired by sign test. **Chi-Square testX^2** was used to test the association variables for categorical data. **r→ spearman correlation :** it evaluates the linear association between 2 quantitative variables (one is the independent var.X, and the other is the dependent var., Y). Value of "r" ranges from -1 to 1

0= no linear correlation

1= perfect positive correlation

-1 = perfect negative correlation

Positive= increase in the independent variable leads to increase in the dependent variable

Negative = increase in the independent variable leads to decrease in the dependent variable.

Results:

Figure 1 shows mean age of the studied cases at presentation was 9.43±3.6 with range of (3-14) years and mean weight was 35.5±12.1 with range of (12-58) kg

This table shows that 36.1% of cases had GBS, 25% of cases had NS, 25% of cases had HUS, 5.6% of cases had SLE and 8.3% of cases had Amyloidosis **Table (1).**

This table shows the mean TLC, mean HB, mean Platelets, mean urea, mean Creatinine, mean calcium, mean C3 and mean Fibrinogen findings of the studied cases **Table (2).**

This table shows that 75% of cases showed improvement after therapy, 16.7% didn't improve and 8.3% died **Table (3)**.

This table shows that number of sessions is <5 in 19.4% of cases, 5-10 in of 66.7% of cases and >10 in 13.9% of cases **Table (4)**.

This table shows that percent of haemorhage was 8.3% and percent of hypotension was 100% of cases **Table (5)**.

This table shows that there is high significant relation between number of sessions and outcome **Table (6)**.

Figure 2 shows that there is high significant relation between the disease and outcome.

Figure 3 shows that there is significant relation between complications and number of sessions

This table shows that there is significant change of urea level, Hg, creatinine and platelets while there is no significant change in other lab findings **Table (7)**.

This table shows that there is NO significant relation between complications and type of replacement fluid **Table (8)**.

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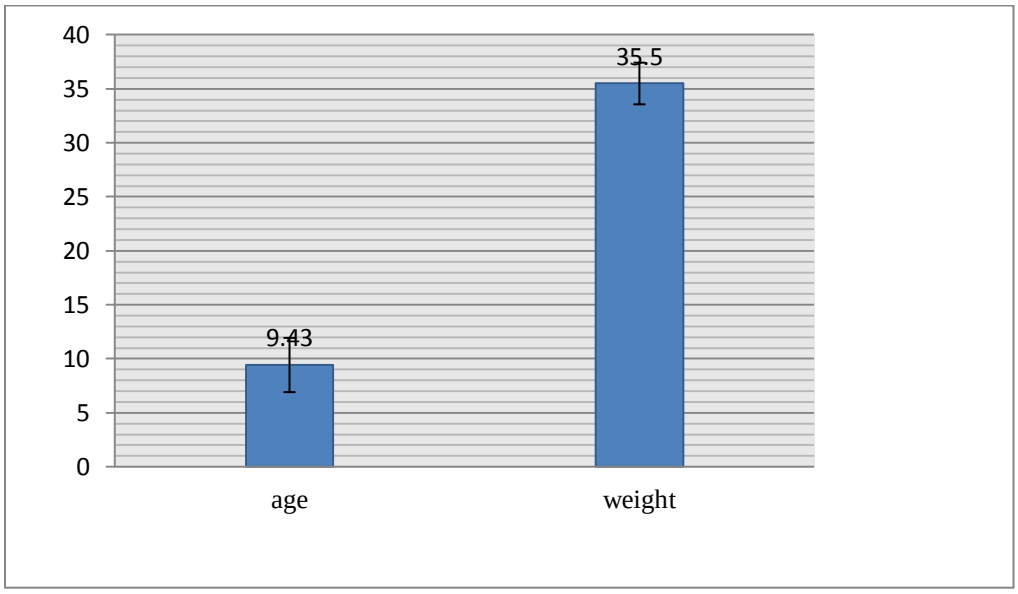

Fig. (1) Mean baseline data of the studied cases on admission

Table (1): Disease presentation on admission:

Disease	No.	%
GBS	13	36.1
NS	9	25.0
HUS	9	25.0
SLE	2	5.6
Amyloidosis	3	8.3

Table (2): Laboratory findings of the studied cases on admission:

Variable	
TLC *1000	
Mean ± SD	11. 8±7.5
Median	10.8
Range	1.2-25.2
HB g/dl	
Mean ± SD	8.8±2.8
Median	9.7
Range	4 -13.8
Platelets 10^3/dl	
Mean ± SD	152.2±184.8

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Median	132
Range	48-176
Urea mg/dl	
Mean ± SD	100±106.4
Median	24.4
Range	8.3-391
Creatinine mg/dl	
Mean ± SD	3.8±4.25
Median	0.6
Range	0.25-11.6
Calcium mg/dl	
Mean ± SD	9±1.4
Median	9.6
Range	6.3-12.5
C3 mg/dl	
Mean ± SD	35±1.4
Median	1.2
Range	0.49-125
Fibrinogen mg/dl	
Mean ± SD	372.2±115.6
Median	360
Range	195-613

Table (3): Outcome of the studied cases:

Outcome	**No.**	**%**
Improved	27	75.0
Not improved	6	16.7
Died	3	8.3

Table (4): number of sessions of the studied cases:

number of sessions		
Mean ± SD	**7.1±1.2**	
	No.	**%**
<5	7	19.4
5-10	24	66.7
>10	5	13.9

Table (5): Complications of the studied cases:

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Complications	No.	%
Haemorrhage	3	8.3
Hypotension	36	100.0
hypothermia	7	19.4

Table (6)The relation between number of sessions and outcome:

Variable	Improved (N=27)	Not improved (N=6)	Died (N=3)	χ^2	P value
number of sessions					
<5	6	1	0	21	**<0.001**
5-10	20	4	0		**(HS)**
>10	1	1	3		

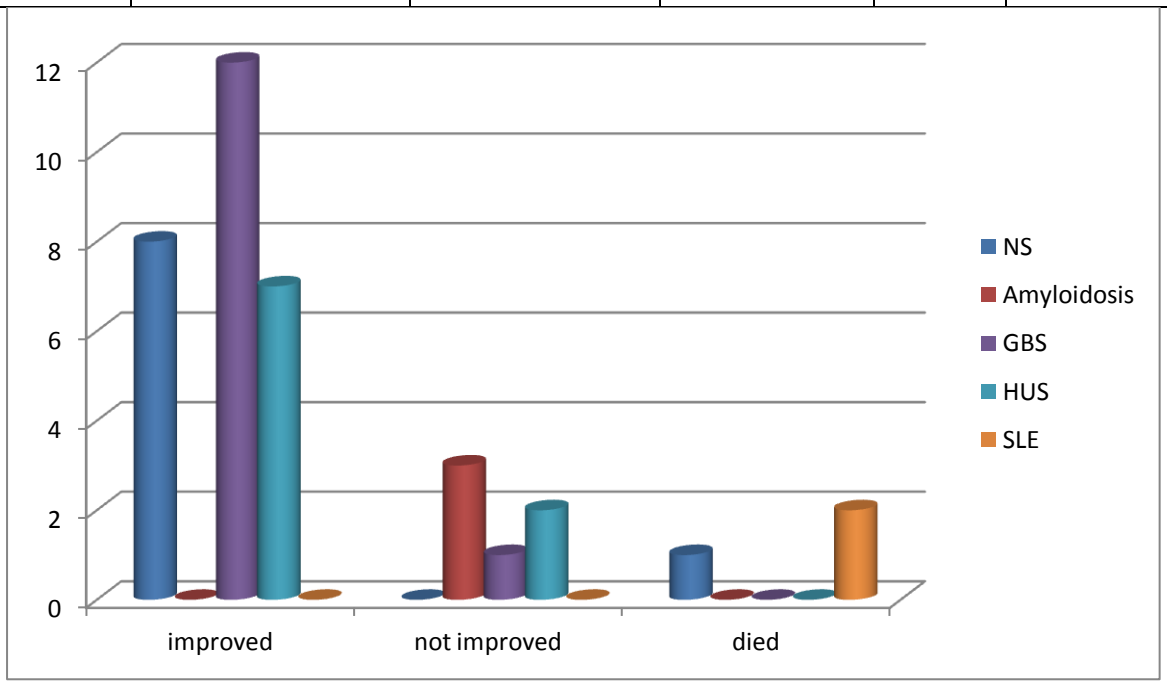

Fig. (2)Distribution of disease condition on outcome

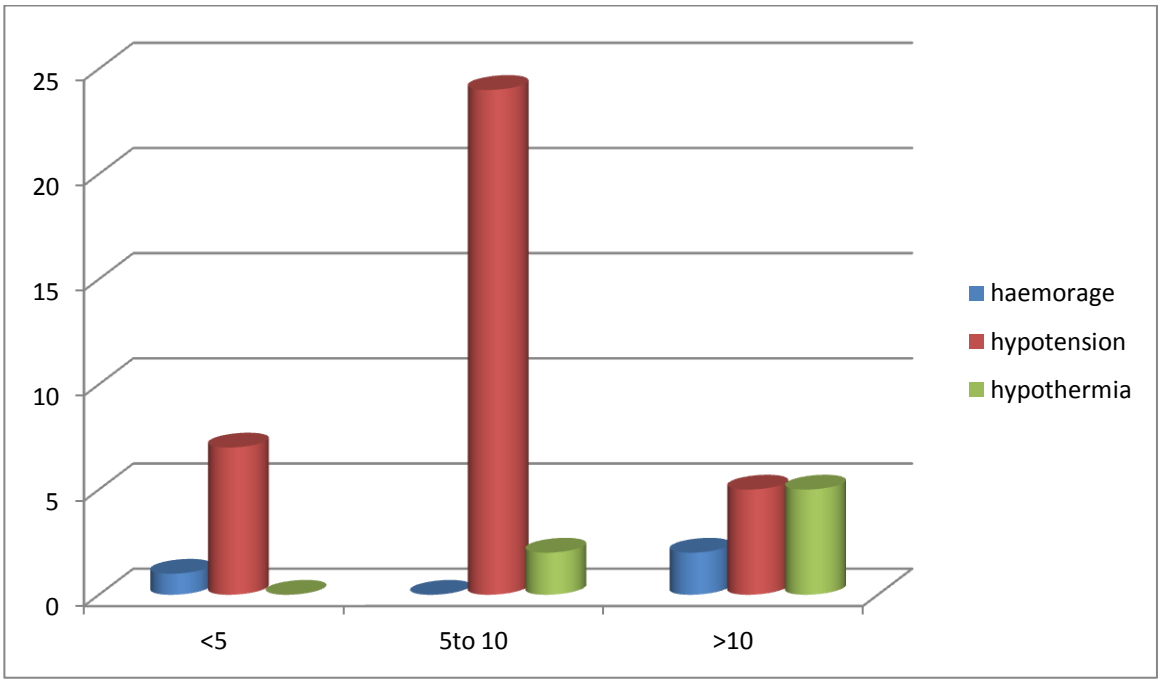

Fig. (3)Distribution of complications on outcome

Table (7) Comparison between on admission and end of relapse laboratory data:

Variable	On admission	End of relapse	Paired t test	P value
TLC 10^3/dl				
Mean ± SD Median Range	11. 8±7.5 10.8 1.2-25.2	13.5±5.9 11.8 7.3-26.5	Wilcoxon rank 1.39	0.164
HB g/dl				
Mean ± SD Median Range	8.8±2.8 9.7 4 -13.8	11.5±1.9 11 8-16.7	30.63	**0.04** **(S)**
Platelets 10^3/dl				
Mean ± SD Median Range	152.2±184.8 132 48-176	265.2±180.6 206.5 48-629	Wilcoxon rank 3.44	**0.044** **(S)**
Urea mg/dl				
Mean ± SD Median Range	100±106.4 24.4 8.3-391	13±21.7 15 40-77.1	Wilcoxon rank 20.65	**<0.001** **(HS)**
Creatinine mg/dl				
Mean ± SD Median Range	3.8±4.25 0.6 0.25-11.6	1.0±2.7 0.83 0.1-8.2	Wilcoxon rank 2.44	**0.046** **(S)**

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Calcium mg/dl				
Mean ± SD Median Range	9±1.4 9.6 6.3-12.5	9.3±1.1 9.3 7.2-12.5	1.08	0.287
Fibrinogen mg/dl				
Mean ± SD Median Range	372.2±115.6 360 195-613	379.8±186.7 351 193-820	Wilcoxon rank 0.931	0.913

Table (8)The relation between complications and type of replacement fluid:

Variable	Saline/albumin replacement (N=29)	FFP (N=7)	χ^2	P value
complications:				
Haemorrhage Hypotension	1(3.4) 28(96.6)	2(28.5) 5(71.5)	Fisher test	0.09

Discussion

The present study included 5 different disease identities; patients with Guillain -barre syndrome (GBS), Hemolytic uremic syndrome (HUS), Nephrotic syndrome (NS), Systemic lupus erythromatosis (SLE) and Amyloidosis. This study revealed that about 36.1% of cases had GBS, 25.0% of cases had NS, 25% of cases had HUS, 8.3% of cases had Amyloidosis and 5.6% of cases had SLE. About 75% of cases showed improvement after therapy, 16.7% didn't improve and 8.3% died. There is high significant relation between numbers of sessions and outcome.

There are many complications that may occur during the procedure. The most common complications are hypotension, hypokalemia, hypocalcemia haemorhage, muscle cramps and numbness of the extremities, metallic taste in the mouth, allergic reactions, bacterial infections and severe suppression of the immune system. At the present study the complication reported were: haemorhage (9.1%) and hypotension in 90.9% of cases. There was significant relation between complications and number of sessions.

The present study reported that there was high significant relation between the disease and outcome. Regarding the patients who were presented by GBS (36.1%) every patient was evaluated pre and post TPE by electromyography (EMG), nerve conduction velocity, latency period, wave amplitude, f-wave and other laboratory investigation as the items of concern in assessment of improvement. It was found that about 12 cases improved (92.3%), one case not improved and no case died during the treatment course.

These results were consistent with the study of **Geelani et al., [2]** which was done to assess about 105 cases who underwent plasmapheresis for various disorders as the main indication for PE was Guillain Barresyndrome (GBS) (31%) followed by Myasthenia Gravis (23%), Rapidly progressive glomerulonephritis (22%), Haemolytic uremic syndrome, Thrombotic thrombocytopenic purpura (20%). GB cases showed the most improvement. The most common complications were paraesthesias and/or cramps (36.1%) and hypocalcemia (7%).There was no mortality related to the

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procedure. The study concluded that the procedure is safe, with only minimal procedure related complications and reported no mortality.

The present study results agreed with the study of **Sidhu et al.,** [4] which included 22 patients underwent 71 TPE procedures. The study group included 13 males and 9 females with their mean age was 36.8 years. Of 22 patients, there were 18 cases of GB syndrome (81.8%), two cases of MG (9%), one case each of thrombotic thrombocytopenic purpura (TTP) (4.5%) and chronic demyelinating polyneuropathy (4.5%). In 18 cases of GB syndrome, complete response was noted in 11 cases (61%), partial response in 3 cases (16%), no response in 4 cases (22%) with an overall response rate of 77% at the end of 10 days follow-up period. One case of CIDP underwent six procedures and recovered completely. This study showed encouraging response rates in neurological diseases.

In addition a systematic meta-analysis reported that TPE was the only treatment for GBS and found to be superior to supportive treatment. Furthermore, TPE was more beneficial when applied within the first 7 days of disease. Studies accounting for a total of 604 patients showed that plasma exchange increased the number of patients being improved by one or more disability grade and the mean grade improvement. Plasma exchange shortened the time on ventilator, and the proportion of ventilator dependent patients was dramatically decreased. During the hospital stay, plasma exchange slightly decreased the risk of severe infections, cardiovascular instability and cardiac arrhythmias. Plasma exchange also had long-term benefits [5].

Regarding the present study, patients with HUS 7 patients out of 9 (77.7%) improved and 2 patients did not improve. These results are consistent with a systematic meta-analysis which had reported that plasma exchange is still the most effective treatment of choice in patients with HUS or thrombotic thrombocytopenic purpura (TTP) and should be considered as early as possible in the disease course. The study reported remarkable decline in mortality with the use of therapeutic plasma exchange which has changed this fatal disease to a mostly curable illness. This role of plasma exchange might be due to its role in the removal of potentially toxic substances from the circulation. Plasma exchange rather than infusion should be considered first-line therapy in situations that limit the amount of plasma that can be infused, such as renal impairment or heart failure [6].

From this study found that 9 patients had NS, 8 patients (88.9%) improved. These results agreed with **Franke et al.,** [7] who treated nine children with cyclosporine-resistant primary FSGS with plasma exchange (PE), two with relapsing FSGS after renal transplantation and seven with FSGS in their native kidneys. Three patients did not respond to PE, but five came into complete remission and one patient achieved partial remission. The patients without response to PE tended to have a longer duration of the disease. They concluded that PE and PIA are a useful option for treatment of steroid- and cyclosporine-resistant FSGS, particularly if applied early in the course of the disease.

Another study reported that PE should be instituted early in recurrent nephrotic syndrome after renal transplantation. The optimum frequency of such treatment still has to be established, especially with regard to its use as long-term maintenance therapy. They suggested that plasma exchange instituted early in the course of recurrent nephrotic syndrome and may be beneficial in some patients with steroid-resistant nephrotic syndrome and FGS [8].

From this study found that 4 patients with SLE, 2 patients controlled and other 2 patients died. The study of **David et al.,** [9] enrolled patients with systemic autoimmune diseases who received TPE**.** In these cases, the main indication for TPE was diffuse alveolar hemorrhage and neurolupus. No TPE-related deaths occurred, and the main complication was hemorrhage, without significant differences among the four types of

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TPE solutions used. The overall outcome was improvement in 41 (62.12%) patients and the study concluded that TPE is safe and effective in patients with severe manifestations of autoimmune diseases.

Plasma exchange can remove putative pathogenic autoantibodies and circulating immune complexes from the blood of patients with systemic lupus erythematosus (SLE). However, their efficacy has only been supported by non controlled and/or retrospective studies. Nonetheless, PE may still be of relevance in some selected SLE patients and as adjunctive therapy, in combination with corticosteroids (CS) and other immunosuppressant(s). Although few SLE patients undergo plasma exchange each year nowadays, adverse events are very rare and recent advances in plasma exchange technologies, like immunoadsorption, might, in the future, counterbalance their cost and broaden their place in the therapeutic armamentarium for SLE [(10)].

By the same manner **Hans et al.,** [(11)] reported clinically significant improvement in the patients with SLE after plasma exchange suggesting that it can be an important component of treatment in patients of SLE with acute life threatening complications in addition to conventional high dose steroid and cytotoxic drug therapy.

Conclusion:

PE can be safely performed in children. It seems that indication for PE and the presence of underlying diseases are affecting the mortality rate. Therapeutic plasma exchange is safe and effective adjuvant treatment for several diseases especially autoimmune diseases with less complications events. PE is a safe treatment method for critically ill children with the appropriate indication, and that the treatment is more effective in patients without comorbidity in addition to PE indication. The analysis of all cases of plasmapheresis in our department showed that the procedure is safe, with only minimal procedure related complications and no mortality.

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