Therapeutic Plasma Exchange and the Clinical Applications

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DEFINITION and the HISTORY

Apheresis is derived from a Greek word meaning to take away by force or seperation. Hemapheresis, a component of blood is removed and the remainder is returned to the donor or the patient, was first performed experimentally on dogs by Dr. Richad Lower in 1666. Plasmapheresis or therapeutic plasma exchange (TPE) may be defined as medical technique by which plasma is seperated from whole blood to be discarded or to be secondarily treated to correct a pathologic condition[1]. It was first done in France in 1902 and in Russia in 1914[2].

The use of TPE by Solomon and Fahey to treat the hyperviscosity syndrome in 1960 is accepted as the start of TPE[3]. By the development of plastic bags and integrally connected tubing system, TPE became a practical reality.

The AIM of THERAPEUTIC PLASMA EXCHANGE

The basic premise of TPE is the removal of the pathogenic or the pathogen related compounds such as monoclonal proteins, cryoglobulins, immune complexes, lipoproteins, antibodies and various toxins, from the blood by using automated cell seperator devices and extracorporeal circulation system (Table 1)[4]. Other potential benefits of TPE are;

1. Unloading of pathologic substances from reticuloendothelial system[5].

2. Stimulation of lymphocyte clones to enhance cytotoxic therapy[6].

3. The possibility of reinfusing large volumes of plasma without the risk of intravascular volume overload.

TECHNICAL ASPECTS

Seperation of plasma from whole blood is the fundemental technical requisite for TPE. It is most commonly performed with centrifugation devices used in blood banking procedures. These devices offer the ad-

Terapötik Plazma Değişimi ve Klinik Uygulamalar

Anahtar Kelimeler: Plazma değişimi, Klinik uygulama.

Key Words: Plasma exchange, Clinical applications.

Table 1. Pathologic substances removed by TPE

Pathologic substance	Disease
Immunoglobulins	Hyperviscosity syndrome Waldenstrom's macroglobulinemia Multiple myeloma
Autoantibodies	Myasthenia gravis Anti-GBM antibody disease Systemic lupus erythematosus Systemic vasculitis
Lipoproteins	Hypercholesterolemia
Circulating immune complexes	Immune complex glomerulonephritis Systemic lupus erythematosus Systemic vasculitis Acute graft rejections
Protein bound substances and toxins	Thyroid strom Amanita phalloides toxins

vantage of allowing selective cell removal. Although centrifugation can be used for this purpose, filtration using a membrane plasma seperator is currently prevailing in most of clinical applications because of ease of manipulation[7].

The whole plasma exchange is the procedure in the cases in which the plasma component is replaced. Hovewer, it is called fractional plasma exchange in the cases in which a partial component of the plasma is divided by a secondary filter, a plasma fractionator, for the purpose of selective removal pathogenic or pathogen related factors that are implicated in disease process. Typical procedures performed for this purpose are, ultrafiltration, cascade filtration and cryofiltration[8,9].

Adsorbtion is also applied for selective or specific removal of pathogenic factors using adsorbant columns. Immunoadsorbtion, which is a process aiming the removal of immunologically related pathogenic factors such as antibodies or immune complexes, is relatively a new technique using staphylococcal protein - A Agarose Column (Immunosorba) and staphylococcal protein- A Silica Column (Prosorba) (Table 2)[10].

As a general rule, large molecular weight compounds equilibrate slowly between the vascular space and the interstitium. Thus, calculations of the rate of removal by TPE can be simplified to first order kinetics (Figure 1). A single volume plasma exchange will lower plasma macromolecule level by 60% (Tables 3,4) (Figure 2)[11].

The following formulas can be used to estimate the total blood volume and plasma volume respectively in adults.

Total blood volume= [70 mL] x [body weight (kg)]

Total plasma volume= [1-hematocrit] x [total blood volume]

The TPE regimen should be determined before the procedure is performed by which pathogenic compound being removed, the desired end point, the amount of plasma to be exchanged, the adjunctive therapies to be performed, total number of procedure and the frequency of procedure. On the other hand, total number and the frequency of TPE to be performed and the benefit of patient from procedure is not clearly defined. Decisions concerning these factors are made according to

Table 2. Practices with immunoadsorbtion

Adsorbant	Substance	System
Active charcoal	Bile acids, intoxication	Human
Heparin	LDL, HDL	Human
Protein A (*Staphylococcus aureus*)	IgG, immune complexes	Human
Concanavalin A	IgM	In vitro
Glomerular bazal membrane	Anti-GBM	Rabbit
DNA	Anti-DNA	Human
Blood group antigens	Anti-A, anti-B	Human
Anti-LDL antibody	IX anticoagulant	Human
Factor IX	IX anticoagulant	Human

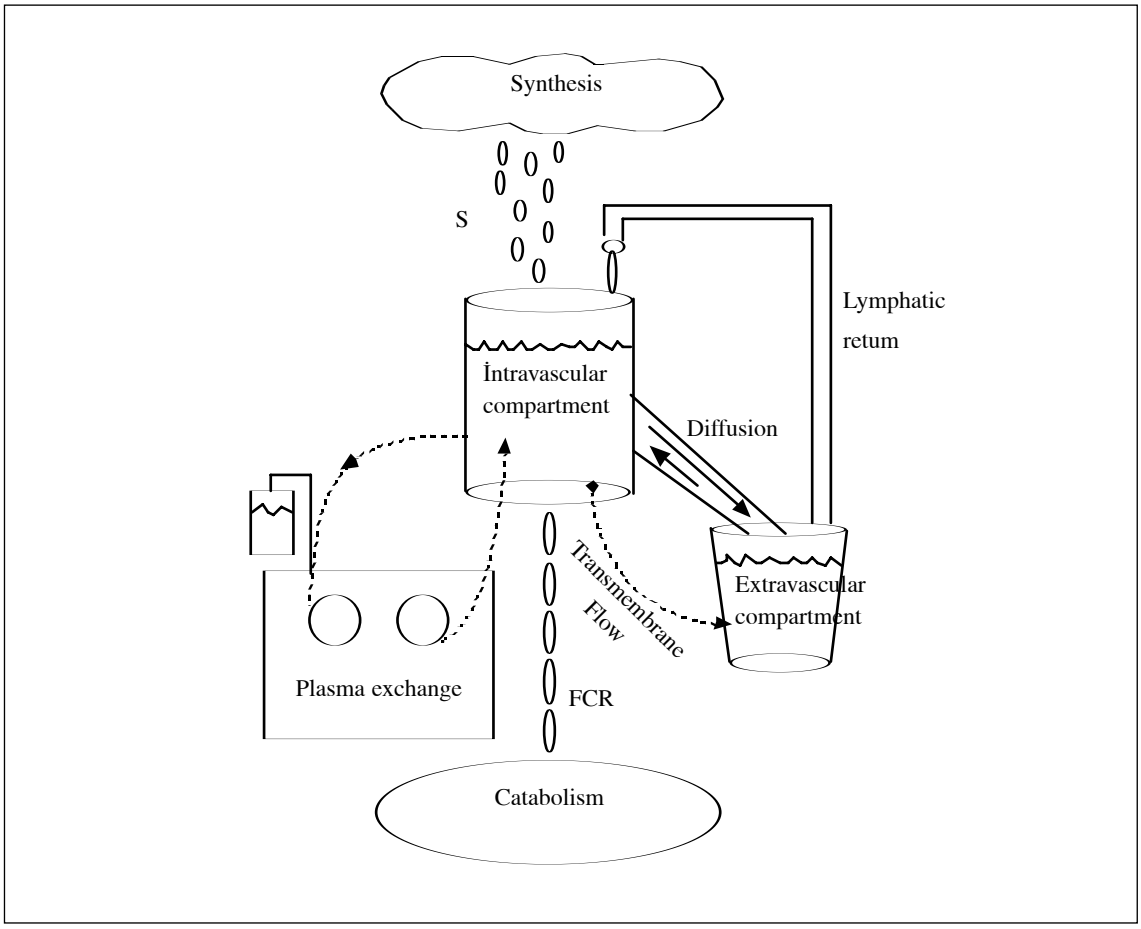

Figure 1. Single compartment model for TPE (Adapted from Weinstein E, Basic Principles of Therapeutic Blood Exchange. In: McLeod B, Price TH, Drew MJ, et al, (eds). Apheresis: Principles and Practice. 1st ed. Maryland: AABB Press, 1997, p.264).

Table 3. Change of the plasma compounds after a single TPE*

Substance	Decrement in basal value (%)	Recovery after 48 hours (%)
Coagulation factors	25-50	60-100
Fibrinogen	63	65
Immunoglobulins	63	45
Paraproteins	30-60	Variable
Liver enzymes	55-60	100
Biluribin	45	100
C3	63	60-100
Thrombocyte	25-30	75-100

* Adapted from Weinstein E, Basic Principles of Therapeutic Blood Exchange. In: McLeod B, Price TH, Drew MJ, et al, (eds). Apheresis: Principles and Practice, 1st ed. Maryland: AABB Press, 1997, p.271.

Table 4. The distribution and metabolic properties of some of the plasma proteins*

Protein	mg/mL↑	M↑(kDa)	Percentage intravascular	FCR↕ (%)	Change in FCR with ↓ concentration	TER (%)
IgG	12.1	150	45	6.7	↓	3
IgA	2.6	$(160)_n$	42	25	Constant	
IgM	0.9	950	76	18	Constant	1-2
IgD	0.02	175	75	37	↑	
IgE	0.0001	190	41	94	↑	
Albumin	42 ± 3.5	66	40	10	↓	5-6
Fibrinogen	2-4	340	80	25	Constant	2-3
C3	1.5	240	53	56		
α_2-macroglobulin	2.6	820	100	8.2	Constant	

* Adapted from Chopek M, Mc Cullough J. Protein and biochemical changes during plasma exchange. In: Berkman EM, Umlas J, (eds). Therapeutic Hemapheresis. Washington, DC: AABB Press, 1980:13-52.

patient's diagnosis, clinical status and laboratory data for each patient individually[12].

The American Association of Blood Banks (AABB) general recommendation for conditions requiring TPE is that one exchange be performed every second or third day, each exchange consisting of 1 to 1.5 plasma volumes, for a total three or five procedures. Hovewer, in some conditions, it may be necessary to perform TPE every or every second day until improvement occurs[13].

In case of a known pathogenic factors to be removed by TPE, the volume of plasma to be exchanged can be calculated according to following formula;

Amount of plasma to be exchanged= plasma volume x plasma concentration of pathogenic compound

Blood samples obtained before and following the procedure gives us to evaluate the efficacy of removal of pathogenic substance. Another point that should be stressed is that, TPE is performed only in intravascular compartment and the efficiency of procedure depends on;

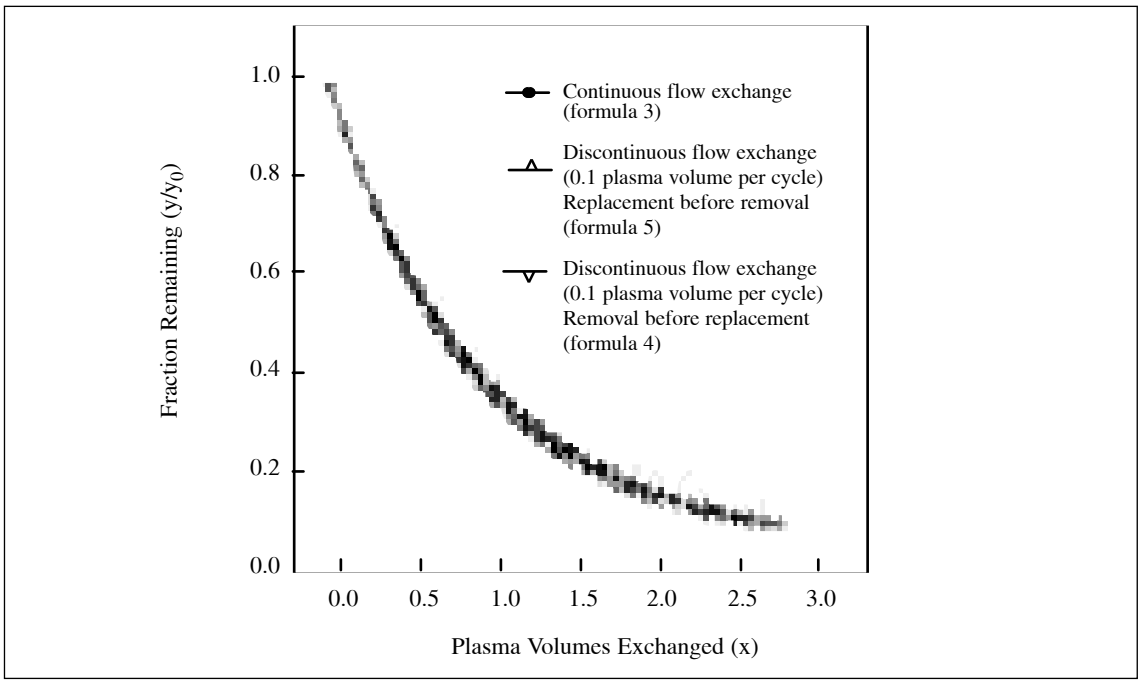

Figure 2. Relationship between plasma volume and the amount of TPE (Adapted from Weinstein E, Basic Principles of Therapeutic Blood Exchange. In: McLeod B, Price TH, Drew MJ, et al, (eds). Apheresis: Principles and Practice, 1st ed. Maryland: AABB Press, 1997, p269.).

1. The volume of blood to be processed,

2. The plasma volume exchanged in each procedure,

3. Total number and the frequency of procedure,

4. The ability of mobilisation, equilibration and synthesis rates of plasma components.

REPLACEMENT FLUIDS

The fluid volume removed by TPE must be replaced to prevent marked volume depletion. Each replacement fluid has advantages and disadvantages comperatively. The optimal choice for replacement fluids often varied with the clinical settings, the disease process involved, availibility, and the cost. Most commonly used replacement fluids are as follows.

1. Albumin (5-20%),

2. Albumin-saline combination,

3. Fresh frosen plasma (FFP),

4. High molecular weight hydroxyetylstarch (Hetastarch).

INDICATIONS

The complexity and the expense of TPE has prompted the development of guidelines based upon clinical data from small series and uncontrolled trials. In 1993, AABB and the American Society for Apheresis (ASFA) through its Extracorporeal Therapy Committee, published the reviews for guidelines for TPE. AABB and ASFA publishes guidelines are updated biannually. Because of the complexity and the expense of procedure, guidelines provide just a framework for clinical decisions and do not aim to divide indications clearly[14,15].

According to AABB guidelines, conditions treated with TPE have been divided into four categories based upon support for clinical efficacy found in literature (Table 5).

Table 5. American Association of Blood Banks (AABB) indications for TPE

Category I: Standard and acceptable under certain circumstances including, primary therapy
• Chronic inflammatory demyelinating polyneuropathy
• Cryoglobulinemia
• Anti-GBM antibody disease (Goodpasture syndrome)
• Guillain-Barre syndrome
• Familial hypercholesterolemia
• Hyperviscosity syndrome
• Myasthenia gravis
• Posttransfusion purpura
• Thrombotic thrombocytopenic purpura
Category II: Sufficient evidence to suggest efficay; acceptable therapy on an adjuctice basis
• Cold agglutinin disease
• Protein- bound toxins (drug overdose, poisoning)
• Hemolytic uremic syndrome
• Rapidly progressive glomerulonephritis
• Systemic vasculitis (primary or due to RA or lupus)
• Acute renal failure due to myeloma kidney
Category III: Inconclusive evidence for efficacy or uncertain benefit-risk ratio
• ABO-incompatible organ or marrow transplantation
• Coagulation factor inhibitors
• Idiopathic thrombocytopenic purpura (protein A adsorbtion)
• Multiple sclerosis
• Progressive systemic sclerosis
• Tyroid storm
• Warm autoimmune hemolytic anemia
Category IV: Lack of efficacy in clinical controlled trials
• AIDS
• Amyotrophic lateral sclerosis
• Chronic ITP
• Polymyositis/dermatomyositis
• Psoriasis
• Renal transplant rejection
• Rheumatoid arthritis
• Schizophrenia

TPE as a NEW THERAPEUTIC MODALITY for SEPSIS

During sepsis, various compounds are released from infectious agents and also from hypoxic tissue including bacterial toxins, immunoglobulins, cytokines, cellular debris, free hemoglobin and myoglobin. These products cause an inflammatory response in the body such as complement system activation, coagulation and fibrinolysis. During a septic shock, activation of these systems may progress into disseminated intravascular coagulation (DIC) and subsequently to multiorgan dysfunction syndrome (MODS) and eventually to death especially in patients with defficient defence system.

The conventional treatment of septic shock includes appropriate antibiotic use, correction of fluid and electrolyte imbalance and in more severe cases the intensive care treatments. Since various compounds are released during these processes, so many studies have focused on to antagonize or minimize the effects of these compounds. Despite the proposed therapies such as the administration of immunoglobulins, antithrombin III, pentoxiphylin and high dose steroids, TPE seems to be the most effective way of removing these compounds from the blood.

As mentioned before, TPE could basically be divided in processing blood unselectively (centrifugation or single filtration) or in a selective way (cascade filtration, ultrafiltration, cryofiltration and adsorbtion). There is only limited clinical exprience in selective therapy by adsorbtion, most of which using polymyxin B as an adsorber. A study by Tani et al, by using adsorbtion in 37 patients with endotoxic shock and 33 control patients, showed significantly better survival in patients treated with adsorbtion as compared to control patients[16].

Most clinical trials have been achieved by unselective plasma exchange. Such approaches have been used in smaller series during the 80s and larger series during the 90s. But none of them were designed as randomized prospective study[17].

Conflicting results have been reported concerning the use of TPE in such patients and prospective, randomized and multicenter studies with larger series are needed.

COMPLICATIONS

A review of reported complications over 15.000 TPE treatments found that adverse reactions were more common with fresh frozen plasma (FFP) than with albumin replacement (20% vs 1.4%)[18]. The most common problems are citrate induced parestesias, muscle cramps and urticaria. More serious complications (eg. anaphylactoid reactions) are also more frequent with FFP than other replacement fluids. The overall incidence of death is 0.03 to 0.05 percent[19]. The common complications are listed below.

1. Hypotension,
2. Citrate induced hypocalcemia,
3. Urticaria,
4. Respiratory distress,
5. Coagulation abnormalities,
6. Infection,
7. Viral transmission with FFP,
8. Anaphylactic reaction to FFP,
9. Drug removal,
10. Problems with vascular catheter,
11. Problems with the use of angiotensin converting enzyme (ACE) inhibitors.

TPE 1998-2002 İBN-İ SİNA HOSPITAL TRIAL

Ankara University School of Medicine Department of Hematology, Apheresis Unit has pioneered the TPE in all over Turkey. Increasing number of TPE procedures were performed to increasing number of patients every year. Figure 3 shows the activity of İbn-i Sina Hospital Apheresis Unit from 1998 to 2002. Table 6 and 7 indicates the patient and the procedure charecte-

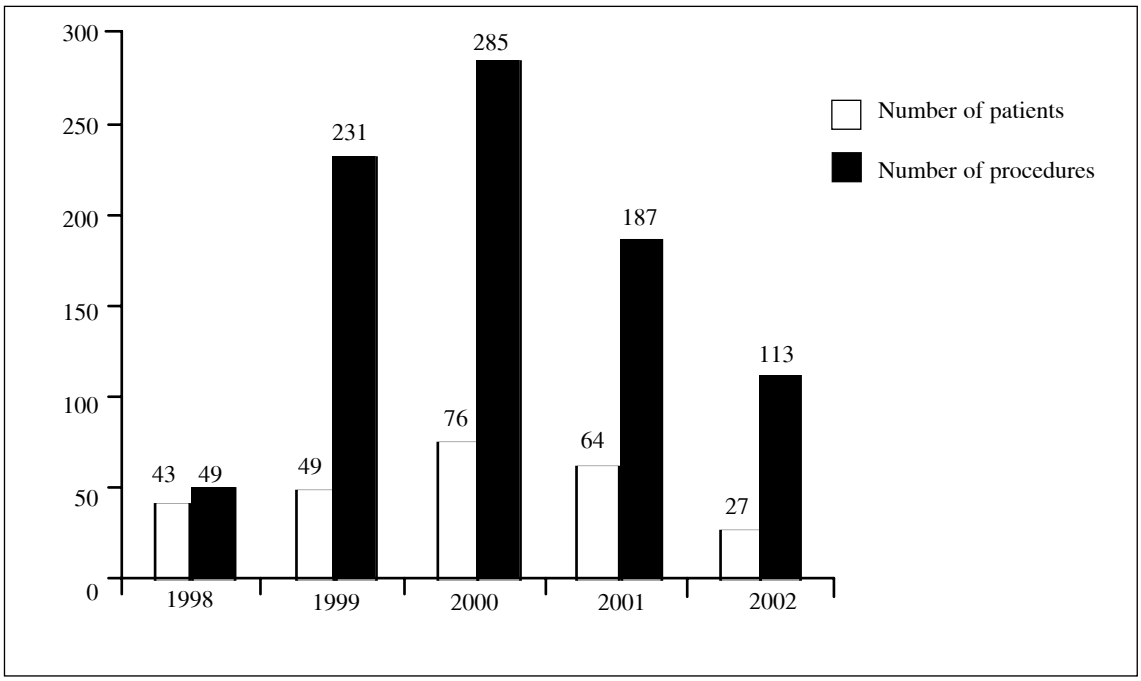

Figure 3. TPE in İbn-i Sina Hospital Orhan Seyfi Sardaş Apheresis Unit (1998-2002).

ristics and diagnosis of patients underwent TPE respectively during the same period. Also the Figure 4 shows the TPE procedures performed according to departments in Ankara University School of Medicine.

TPE in TURKEY

Turkish Apheresis Group (TAG) has maintained a national registry for apheresis activities since 1997. According to the data obtained from TAG, a total of 172 patients (female/male: 73/99) underwent TPE with a total number of 869 procedures at 21 different centers in Turkey in 1998. The median age of patients involved in the procedures was 38 ranging from 14 to 68. The number of procedures per patient was 4 and the most common indications for TPE were thrombotic thrombocytopenic purpura with 48 patients, myasthenia gravis with 36 patients and Guillain-Barre syndrome with 32 patients. Among all procedures 435 were performed using albumin 5%, 347 with FFP and 87 with HES 3%[20,21].

Table 6. Charecteristics of the patients and the procedures (1998-2002)

Number of patients	: 259
Female/male	: 134/125
Age (median)	: 41.3(14-75)
Number of procedures	: 865
Procedure perpatient	: 3.33(1-17)
Replacement fluids	
Hydroxuethylstarch (HES)	: 319
Albumin	: 299
Fresh frosen plasma (FFP)	: 254

CONCLUSION

TPE is an ever developing treatment modality with its new clinical applications. Hovewer, in Turkey, not also because of the insufficient qualified staff but also the inadequate colloboration with othert clinical de-

Table 7. Diagnosis of patients underwent TPE in İbn-i Sina Hospital in 1998-2002

Diagnosis	Number of patients	Number of procedures
Myasthenia gravis	92	287
TTP	27	155
Multiple sclerosis	13	60
Multiple myeloma	38	96
Progressive systemic sclerosis	9	55
Polymyositis & dermatomyositis	9	42
Guillain-Barre syndrome	14	38
Immune hemolytic anemia	9	31
Pemphigus vulgaris	4	19
ITP	4	17
Sepsis	9	15
Cholestasis	6	14
Disseminated intravascular coagulation	8	14
Hypoxic encephalopathy	2	10
Systemic lupus erythematosus	4	8
CNS vasculitis	3	8
Transverse myelitis	1	5
Rheumatoid arthritis	2	4
Rapidly progressive glomerulonephritis	4	4
Intoxications	2	3

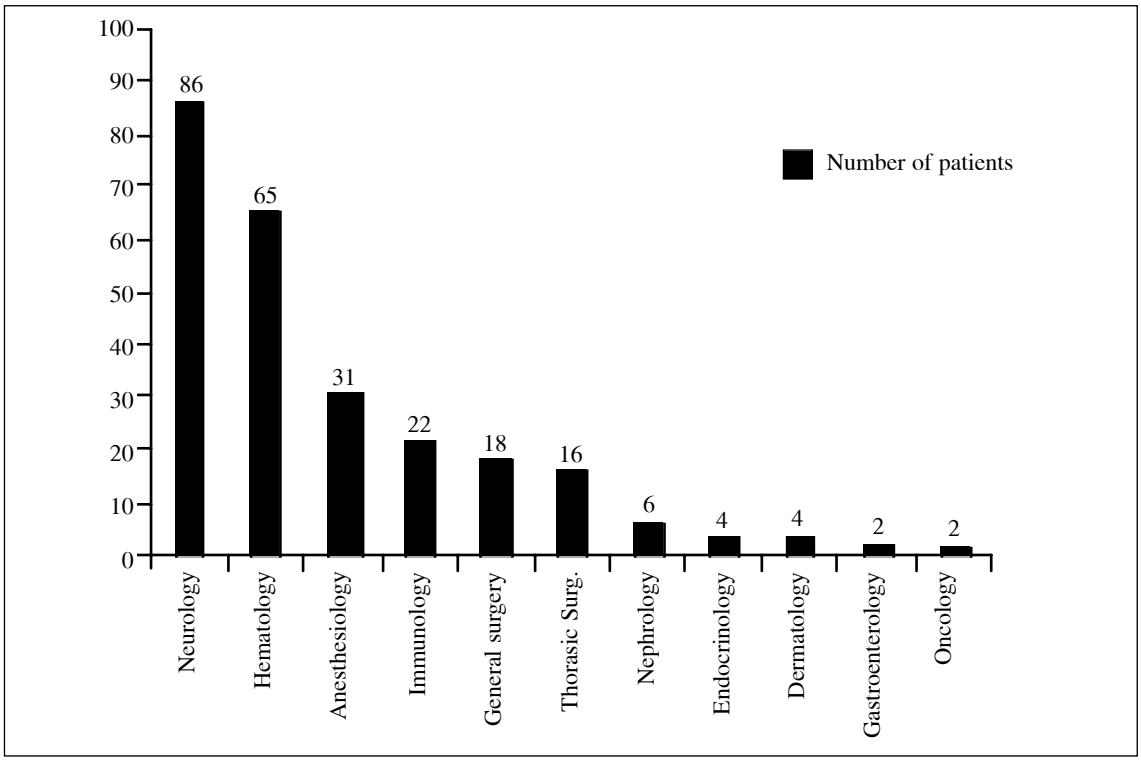

Figure 4. TPE according to departments in İbn-i Sina Hospital (1998-2002).

partments, is far away from exact clinical practice. According to data obtained from apheresis subcommittee of Turkish Hematology Association, TPE performed per person is far less compared to industrialized countries (Table 8)[21].

To improve the amount and the spectrum of TPE in our country, a close collaboration should be provided first with departments of nephrology, neurology and rheumatology and also with other departments.

Additionally, to standardize the TPE procedure and to gather information from different centers, a centrally operated recording system is mandatory. That's the way to follow up of all procedures performed[21].

Table 8. TPE in the world 1998

	Total number of patients	Total number of procedure	TPE perinhabitant
Canada	720	8392	?
France	898	8100	1.3×10^{-4}
Sweden	439	3562	3.5×10^{-4}
Turkey	172	869	1.3×10^{-5}

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