The summary of the doctoral thesis

“Implications of plasma loss at the beginning of the therapeutic plasma exchange procedures”

Therapeutic plasma exchange (TPE), better known as plasmapheresis, represents an extracorporeal blood purification method whereby plasma is separated from the rest of the blood elements: erythrocytes, leukocytes, platelets and its replaced with fluids (albumin, fresh frozen plasma, crystalloids). The process of plasma separation from the blood, at the present time can be achieved by 2 techniques: centrifugation or filtration. The devices that perform these techniques have evolved exponentially in the last 20 years, both in number and performance. The reason for this increase is justified by the large number, of pathologies existing in the world at the present time which have as an indication the plasma clearance.

With the diversification of the activity of the intensivists in the domain of plasma purification and not only (hemodiafiltration, extracorporeal oxygenation, decarboxylation) new challenges have arisen but also new needs. The purchase of devices that achieve plasma clearance has increased the number of patients who benefit from their usefulness. At a normal TPE session, about 20 PPC bags (freshly frozen plasma) are needed, we need 20 donors. The insufficient number of donors together with compatibility issues, the effectiveness or availability of replacement solutions has given rise to some challenges. The question arises what can we do if we do not have the necessary amount of substitute for therapeutic plasma exchange sessions? This thesis aims to provide an answer to the question and to analyze the implications that this answer has.

At the ideal treatment mode (100% purification), we would be able to remove the entire amount of plasma containing pathogenic elements and then replace it with the same amount of plasma that does not contain these pathogenic elements. This ideal model cannot be applied to the human body. The therapeutic plasma exchange is made "drop by drop" (a drop of plasma with pathological elements is lost, a plasma drop is administered without these elements).

In the first part, the thesis investigates a mathematical model of the treatment of substances by TPE when the drops have different values and objects

the impact on the plasma concentration of these substances. In the second part of the thesis, the impact of the plasma loss at the beginning of the TPE session is investigated, in the light of the therapeutic and economic efficiency. The last part of the research is allocated to the patient profile to which this method can be applied through plasma loss and the safety for the identified patient.

The questions to which I offer an answer in the research from this doctoral thesis are:

1. What is the amount of plasma that a patient can lose without receiving a replacement?
2. Does it bring any benefit in terms of cost / efficiency ratio, plasma loss at the beginning of the session?
3. How safe is this procedure for hemodynamic stable patients?

In the first part the objective was to study the correlation between the mathematical form of a chemical that we want to lower its initial concentration by the regressive method and the purging of the body's toxic present chemicals that need to be eliminated. We developed a chemical model, by which, to a given volume, with a certain (X - concentration %) dissolved substance in a container, the initial solvent, without solvit, is added (concentration 0%) with an equal rhythm to the one that is lost from the used container. The solution that will be lost will contain less and less concentrations of solvit, compared to the initial value X%. At the same time, the concentration of our chemical model will decrease. We applied a regressive mathematical formula to this model in order to calculate the concentration in the container in each moment.

At the same time, we conducted treatment sessions in patients in which certain substances need to be eliminated, a procedure that complies with the described chemical model. We have demonstrated that at the same volume of 0% solvit wash, the substance purging with X% concentration is more effective, if the procedure starts with an initial loss of concentrated substance, with ulterior volume replacement. Laboratory data confirms the mathematical model in patients who started the procedure with plasma loss. The developed chemical model demonstrates that the initial loss of substance, hastens the decrease of the initial concentration, especially as the loss is higher at the beginning of the procedure if we use the same replacement volume without the substance in the initial solution. This

model can be applied in plasma treatment methods in order to study the patient's safety and the amount of plasma the patient can lose at the beginning.

Since March 2015 to June 2019, 258 TPE sessions were performed in the Intensive Care Clinic of the Timisoara County Hospital, 72 patients, 22 DFPP sessions in 8 patients and over 400 CRRT sessions. Most of these procedures have been included in records for extracorporeal therapy methods.

Most cases with TPE or DFFP were from the sphere of neurological pathologies: myasthenia, acute (more frequent) or chronic poliradiculonevritis, transverse myelitis, multifocal poliradiculopathy, encephalitis, sd Eaton-Lambert, where the intricate mechanism is autoimmune, and where the treatment consists of plasma Ig purification from antibodies against their own tissues belonging to the central and peripheral nervous system.

The following pathologies in the nephrological domain are frequent: systemic lupus erythematosus and vasculitis; then the hematologic ones (thrombotic thrombocytopenic purpura), acute hepatitis, hypertriglyceridemia and sepsis. Our group also included 5 patients with high plasma mercury values that we considered Hg poisoning and we tried to treat through TPE or DFPP sessions.

All 258 sessions were monitored clinically and paraclinically in the intensive care unit. Standard monitoring (BP, HR, EKG, SpO2) was used in all patients, at less than 5% invasive monitoring of TA was used. Randomly, when we considered that the patient's hemodynamic status was stable, we started the TPE procedures only through plasma loss till the patient starts to become hypotensive. This loss was not determined exactly from the beginning but only not to be greater than 1000 ml in the first hour. The rate of loss was set between 500 and 1000 ml per hour. The machines with which the sessions took place were: Prismaflex with TPE 2000 kit - 160 sessions, Infomed 440 with Granopen plasma filter - 88 sessions and BBraun Omni TPE - 10 sessions.

Depending on the amount of plasma lost at the beginning of the TPE session, the group of 258 patients was divided into four groups:

- Group 1 - no plasma loss (loss 0) - 94 procedures
- Group 2 - with low plasma loss (below 400 ml) – 28 procedures
- Group 3 - with moderate plasma loss (between 400-700 ml) – 67 procedures
- Group 4 - with high plasma loss (over 700 ml)- 69 procedures

We evaluated the hemodynamic impact that the plasma clearance procedures with or plasma loss has on the patient and I concluded:

- In the procedure of TPE the patients show a statistically significant decrease of tension, but whose gross value does not represent a serious alarm for the patient's health in the studied group. The reason for safety is given by the fact that the compared groups are made up of patients with an average of 52 years, without hypotension, who begin treatment at a TAM of 105 mmHg.
- The hypotension given by the TPE procedure in which the substitute used is only albumin is greater than that given by the TPE procedure in which the substitute used is only fresh frozen plasma (PPC).
- At an average plasma volume of 2990 ml there was an average loss of 852 ml, equals 28.5% of the plasmatic volum (VP).
- **A hemodynamically stable patient may lose plasma at the beginning of the TPE session**
- The amount of plasma that a patient may lose is variable and sometimes difficult to predict.
- Hemoglobin and hematocrit increase togheter at a ratio of 1: 3.1 with loss of plasma.
- At a loss of 30% of VP, Hb and Ht increase by 15-20% (from 13.08% to 15.8% hematocrit, respectively from 37.55 g / dl to 47.45g / dl hemoglobin).
- 95% of patients may lose 400 ml of plasma, equals 15% of VP without significant hemodynamic impact (TAM decreases from 105mm Hg to 84 mmHg)
- 85% of patients may lose 700 ml of plasma, equals 25% of VP with minor hemodynamic impact (TAM decreases to 76 mmHg)
- 60% of patients may lose 1000 ml of plasma, equals 30% of VP with medium haemodynamic impact (TAM decreases to 64 mmHg)
- The remain percentages up to 100% belongs to the patients who can no longer lose plasma (5% may not lose 500 ml, 15% may not lose 700 ml, 40% may not lose 1000 ml) in this group of hemodynamically stable patients at the first TPE procedure.
- Lowering TAM below 65 mmHg requires stopping plasma loss and supplementation with albumin, crystalloids or if the situation requires vasopressor support

- HR (heart rate) evolution in this group did not show severe bradycardia (AV <50 / min) or tachyarrhythmias (AV> 130b / min), the values being between 51 and 129 b / min
- HR is generally characterized by an increase of 20-30% at the maximum loss of 30% of the VP, and by 10% at a loss of 15% of the VP.
- The amount of plasma that can be lost we proposed that 400 ml is a **safety volume (15% of the plasma volume)** for a patient of 70 kg and 700 ml should be a **volume of tolerance (25% of plasma volume)**. By these conclusions I answered the questions launched as hypotheses at the beginning of the research.

In the last part of the doctoral thesis I presented the particularities of the plasma treatment sessions in Timisoara County Hospital in Intesive Care Department:

- In last 4 years a large number of 258 TPE sessions were performed, which were monitored.
- The typical patient who performed TPE is a 52-year-old 75 kg patient, hemodynamically stable with TAM of 108 and HR of 82 b / min, with slight respiratory failure. The Apache score at admission is below 10, but there were also 7 patients with tracheal intubation, 5 coma patients and all of them on vasoactive support. Mortality among these patients is not related to the therapy performed but to the severity of the underlying disease. 3 patients with myasthenia died due to complications of intensive care stay, 2 patients with severe hepatic failure, one patient with possible autoimmune encephalitis and one patient with severe lupus eritematosus.
- Myasthenia gravis and poliradiculonevritis represent 2/3 of the treated pathology
- The Prismaflex device is preferred by our team because:

  - is the best known TPE machine by the collective
  - is extremely reliable, performs other procedures as well: CRRT, decarboxylation, liver treatment
  - extremely easy to use start kits
  - can achieve losses of 1000 ml per hour

- can at any time receive controlled predilution with crystalloid solutions or even with citrate
- alarms are predictable and problems that can be resolved

- The serial connection of plasma bags through increases the comfort of the medical staf performing the procedure
- The volume of average substitute was 0.9xVP but due to the loss of plasma, its value increased to 1.1xVP
- The time required for a TPE session was 4 hours and 11 minutes. If we take into account other times required for this procedure such as catheter assembly, circuit mounting and priming (on average 30 minutes), solving problems related to flow rates, pressures, alarms or even changing replacement bags, we will conclude that for a TPE session we need to reserve about 5 hours!
- Although heparin is extremely easy to use, it does not have the same effectiveness in protecting the filter as when using citrate
- It is not necessary to monitor the clotting times
- The main adverse effects reported in our group of patients were hypotension, allergic plasma reactions, pruritus, hypocalcemia manifested by paresthesias or muscle cramps, fever, and cardiac arrhythmias.
- Problems related to the dialysis catheter have been reported, mainly due to the insufficient flow that it has performed, and in isolation, there have been reported bleeding, hematomas, thrombosis or infections.

In this period of time, 22 DFPP (double filtrate plasmapheresis) procedures were close monitored in our hospital. The results obtained after analysing the 22 sessions of DFPP shows that hypotension occurs in the sessions where there are several flushes (over 2), or where the second filter is of smaller caliber (10kDa). To prevent it, the intervention is done early by administering human albumin 5-10% as a substitute, especially when we want to perform a more aggressive treatment with Medopen 10 filter, and where the pressure curve in the plasma separator reaches quickly the value of 150 mmHg, so where are we supposed to have more of his flushes. If the first flush occurs faster than 20-30 minutes we can expect DFPP treatment to consist of more than 4 flushes.

The research of the group of patients with mercury poisoning proves that the sessions of plasma treatment by simple plasma exchange or double filtration are effective in eliminating the plasma mercury in both acute and chronic Hg poisoning. The utility of eliminating plasma mercury through TPE or DFPP is greater if it is done in acute intoxication where we have blood mercury above normal values. In chronic poisoning, where mercury is already fixed in different tissues, the efficacy of plasma clearance procedures is lower for the disease itself, but may have an important role for autoimmune symptoms that some patients may manifest.

12 plasma clearance procedures with TPE or DFPP were performed. These are effective for patients with hypertriglyceridemia (HTGL) by significantly decreasing plasma triglycerides but whose decrease cannot be accurately predictable by volume. plasma changed.

The economic advantage

We proved that if we try to calculate what are the quantities of substitute that we save by realizing plasma loss at the beginning of the procedure, to have the same treatment efficiency we will obtain the following results.

At a loss of the beggining of:

200 ml will save 350ml (1.5 PPC bags)

500 ml will save 750ml (3 PPC bags)

700 ml will save 900ml (4.5 PPC bags)

1000 ml we will save 1400 ml (7 PPC bags) .. 7x150Euro about 1000 **€**

If we extrapolate this data in our group of patients between 2015 and 2019 we have managed to save:

• 159.74 liters of plasma

or

• 798.7 PPC bags

or

• 400 bottles of human albumin 20% of 100 ml

or

• **150,000 €**

In conclusion, the doctoral thesis demonstrated the effectiveness and safety of the TPE and DFPP procedures performed. If the TPE procedure started with the

loss of plasma then we will get a more efficient treatment with the same changed plasma volume. Plasma loss from the beginning of the procedure should be monitored on an intensive care unit. The amount of plasma that can be lost is between 15 and 25% of the patient's plasma volume. Plasma loss at the beginning of TPE brings an economic benefit by saving expensive substitute.