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Comparison of different Lp (a) elimination techniques: A retrospective evaluation

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ABSTRACT

Lipoprotein (a), abbreviated Lp (a), is accepted as a potential selective or additional risk factor for premature atherosclerosis. Though it may be considered to be closely related to low density lipoprotein, so far attempts to keep it under control with diet or cholesterol lowering medications have failed. Thus, extracorporeal elimination is the only effective treatment approach for patients with premature atherosclerosis. As different techniques for differential elimination such as precipitation, adsorption and filtration exist, it appeared of interest for us to retrospectively evaluate adsorption and filtration procedures in their capacity to lower Lp (a). Four patients with selectively elevated Lp (a) and eight patients with familial hypercholesterolaemia and additional elevated Lp (a) could be evaluated. All patients had Lp (a) values of 80–120 mg/dl without treatment in common. Different plasma or whole blood volumes were processed to obtain 30 mg/dl Lp (a) as post-treatment target values. In patients with a selective elevation Lp (a)-apheresis, as developed from Prokovski, was the most potent elimination procedure, decreasing the Lp (a) by at least 81% of the initial value after processing 6 L of plasma followed from LDL-(immune) apheresis with 71%. Plasma differential filtration using the Kuraray LA 4 filter decreased Lp (a) by 70% processing only 3.4 L, however was less selective and limited by the loss of fibrinogen and other high molecular weight proteins. In patients with familial hypercholesterolaemia and Lp (a) elevation in a range of 80–120 mg /dl LDL-(immune) apheresis removed >80% of Lp (a) processing 6 L of plasma whereas if 5 L were processed a removal of 76% was comparable to liposorption. Neither whole blood perfusion (DALI, Fresenius) nor filtration applying the Kuraray LA 5 filter was able to reach the desired target values.

1. Introduction

Lipoprotein (a) is an LDL-like particle which was described as having an atherogenic [1–8] and thrombogenic [9–14] potential. Whether Lp (a) increased the vascular risk only in combination with other risk factors such as increased LDL-cholesterol, low HDL-cholesterol, diabetes and others or could also be considered *in a selective isoform* as a genetically determined independent, isolated cause of atherogenesis [15–27] is under debate. Increased Lp (a) may be of pathogenetic importance for kidney diseases [27–34], hypertension [35], diabetes [36–38], stroke [39,40] pulmonal hypertonia [41] and aneurismal disease [42].

With the development of Lp (a)-apheresis [43,44] the earlier claim, that there is "no treatment" for an elevated Lp (a) other than the elimination of additional risk factors is not valid any more. The term Lp (a)-apheresis should not be misused for other techniques also lowering Lp (a) (comparable to the confusion observed with the term LDL-apheresis). Procedures lowering both LDL-cholesterol and Lp (a) by 50–60% may clinically not suffice as it may delay progression of atherogenesis rather than preventing it.

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Such prevention appears more likely to be obtained by Lp (a)-apheresis decreasing the pre-apheresis values about 80–90% and obtaining post-treatment target values of 30 mg/dl with a better promise of optimal clinical efficacy. However, the rather rapid rebound needs to be taken into consideration.

2. Structure of lipoprotein (a)

Lipoprotein (a) or abbreviated Lp (a) may be considered as an inherited, genetically determined special form of low density lipoprotein, which may explain the atherogenic potential. However differences in structure are obvious, as it also has a structural relationship to plasminogen, which may lead to an interference with the coagulation cascade.

The molecule consists of a core of cholesterol, phospholipids and apolipoprotein B 100 (apo b) which is linked to apolipoprotein a (apo a), a high molecular weight glycoprotein. Apo a is synthesized in the liver cells, but it is assumed that the binding with the LDL particle is an extracellular process. The way the particle is segregated is hardly known. The presence of apo a explains why it differs from LDL-cholesterol. Apo a presents as an external "cringle" (cringle = Danish brezel) which surrounds the apo B core to which it is bound by a disulfide bridge. Lp (a) is a very heterogenous particle (up to 30 isoforms) of different densities and molecular weights. The cringle structure of apolipoprotein A is homologous to plasminogen and enables the interference with the coagulation cascade.

3. Aim of the study and methods

We evaluated retrospectively four patients with selectively elevated Lp (a) and premature atherosclerosis treated under the following conditions:

- Initial range of Lp (a) between 80 and 120 mg/dl.
- Application of the same procedure for each patient (Lp (a)-apheresis, LDL-(immune) apheresis, secondary plasma filtration) whereas the processed plasma volume varied from 3.4 to 6 L.

All patients had a severe premature atherosclerosis with advanced coronary heart disease. Also eight patients with a combination of familial hypercholesterolaemia and elevated Lp (a) ranging from 80 to 120 mg/dl Lp (a) prior to apheresis and suffering from advanced coronary heart disease were evaluated if treated under the same conditions but with LDL-(immune) apheresis, liposorption, whole blood perfusion and secondary filtration though using a different filter.

All treatments were performed at weekly intervals (except for one patient with a selectively elevated Lp (a) who is treated every two weeks) attempting to reach Lp (a) post-treatment values of 30 mg/dl, The rebound was estimated calculating the average values after the treatments and comparing them with the average pre-treatment values.

Table 1
Maximal decrease in patients with *selectively* elevated Lp (a) under apheresis therapy: comparison of different technologies (range of Lp (a) prior to treatment: 80–120 mg/dl; target value: 30 mg/dl).

Procedure	Treatments (N)	Volume processed (L)	Decrease	
			(mg/dl)	(%)
Lp (a)-apheresis	12	6	80	81
	72	5	75–83	79
	16	4	65	69
LDL-apheresis	10	6	79	71
(Immuneapheresis)	18	5	54	60
Filtration (Kuraray LA 4)	38	3.4	69	70

The rebound of these patients was in a range of 10–18 mg/dl per day.

Table 2
Maximal decrease of Lp (a) under apheresis therapy in patients with familial hypercholesterolaemia and elevated Lp (a): comparison of different technologies (range of Lp (a) before treatment: 80–120 mg/dl; target value: 30 mg/dl).

Procedure	Treatments (N)	Volume processed (L)	Maximal decrease total cholesterol (%)	Maximal decrease Lp (a) (%)
LDL-apheresis	16	6	72	82
(Immuneaph. P)	30	5	48–51	76
	9	4	67	71
(Immuneaph. M)	6	5	51	56
Liposorption	42	5	65	77
	28	4	54	69
Whole blood	16	5	56	65
Filtration (Kuraray LA 5)	9	3.2–3.6	53	53
(Kuraray LA 4)	18	3.5	42	64

The rebound was figured to be in a range of 8–17 mg/dl per day.

4. Results

The results are shown in Table 1 for patients with a selectively elevated Lp (a) and in Table 2 for patients with familial hypercholesterolaemia and an elevated Lp (a) as an additional risk factor. It is obvious that both immune apheresis procedures are most efficacious and as they can be re-used not only during the individual treatments but also from one treatment to the other for the same patient are most economic.

The rebound as drawn from these data is similar in both groups, however the divergence is considerable and more data may be necessary to obtain a more patient oriented individual insight.

5. Discussion

The indication for the extracorporeal treatment of patients with a selectively elevated Lp (a) is under debate.

Lp (a) values exceeding the 75th percentile are at high risk for cardiovascular disease, demonstrated from studies such as PRIME, [45], ILSA [46] and others [53]. This information is also supported from experimental data. As patients at high risk due to an elevated Lp (a), both as co- or independent risk factor, are without convincing drug

therapy so far, extracorporeal elimination such as regular Lp (a)-apheresis is the therapy of choice and without alternative.

For all patients with a selectively elevated Lp (a) it is obligatory to eliminate additional risk factors such as smoking, hypertonia, obesity and others to be eliminated. However this is no treatment but prerequisite.

As we have seen patients with selectively elevated Lp (a) values of more than 250 mg/dl without premature atherosclerosis we recommend that such patients remain under cardio-angiological control once per year but without treatment. If the development of premature atherosclerosis with clinical relevance can be demonstrated during the observation period, early treatment should be initiated even if no further risk factors can be found. It is beyond debate that patients characterised from a selectively elevated Lp (a) e.g. >80 mg/dl, premature atherosclerosis without further risk factors and particularly if clinically symptomatic with an early vascular disease (e.g. myocardial infarction underneath 35–40 years of age) must be treated with Lp (a)-apheresis.

For patients with *familial hypercholesterolaemia in combination with elevated Lp (a)* also no treatment alternative exists, after diet and cholesterol lowering medications have exhaustively been applied.

The thrombogenic potential if of clinical relevance for such patients may also be taken into consideration.

Whether the lack of controlled trials providing for final evidence of the clinical value of an extracorporeal elimination of Lp (a) in severely sick patients and patients at high coronary risk appears to be a formality for reimbursement or justifies Lp (a)-apheresis with all consequences for the maintenance of an optimal quality of life and life expectancy may not only be considered as a problem of generalised consideration and bureaucratic formalism but needs also an individualised, thoughtful decision as an issue of medical ethics.

In analogy of our 28 years experience with the original LDL-apheresis and the survival of patients under optimal treatment conditions we favour post-treatment target values of 30 mg/dl rather than referring only to a decrease expressed in percentage as this approach appears to promise a better or even an optimal clinical efficacy. Nevertheless, if such percentage is taken as a measure it should exceed a decrease of at least 70%. However, the rather rapid rebound needs also to be taken into consideration.

For patients with a selectively elevated Lp (a), the choice of the optimal treatment technique depends on the initial level of Lp (a). Lp (a)-apheresis is the most potent elimination procedure which guarantees optimal post-treatment values, but needs the procession of higher plasma volumes, whereas other techniques such as plasma differential filtration eliminate other plasma components as well and have a limited capacity suitable for the treatment of patients with lower Lp (a) values (underneath 80 mg/dl).

FH patients with an additional elevated Lp (a) are more difficult to treat, as LDL-apheresis columns if used in a repetitive cycling approach may obtain optimal post-treatment values of LDL-cholesterol but only suboptimal post-treatment Lp (a) values. Thus technical considerations for an optimal decrease of both risk factors for the best treatment of these patients are necessary.

As 30 mg/dl are considered as "normal" one should consider this value as target for an optimal patient treatment rather than restricting oneself to a limited percentage of Lp (a) elimination (e.g. 60%). The treatment should completely eliminate Lp (a) as the risk factor, if it is technically possible, to maintain, an optimal quality of life and halting the progress of premature atherosclerosis for an optimal survival.

This evaluation cannot replace a controlled trial, particularly as it restricts itself to a retrospective approach and the comparison of different treatment techniques. Also, it comprises only a limited number of comparable procedures. Nevertheless, it contributes to the selection of the most efficient and most economic elimination procedure.

Variations of the measurement procedures [47–52] with new insights into the importance of the size heterogeneity together with other issues raised again discussions whether Lp (a) increased the vascular risk only in combination with other risk factors such as increased LDL-cholesterol, low HDL-cholesterol, diabetes and others or could also be considered as a genetically determined independent, isolated cause of atherogenesis. Such discussion is directly related to the indication for extracorporeal Lp (a) lowering therapy.

Numerous procedures have been applied to estimate the efficacy of extracorporeal cholesterol lowering therapy. The most convincing evidence is the survival of patients under long term treatment. Patients with selectively elevated Lp (a) are of special interest.

One of the four patients is now under regular therapy for 15 years without obvious signs of progression, whereas the other three patients are treated only for 1–1/12 years so far and do not yet allow to draw any conclusion. Thus, a controlled trial using Lp (a)-apheresis for patients with Lp (a) concentrations of more than 80 mg/dl is desirable. However, due to the complexity of the problem one should not underestimate the problems of designing such trial.

6. Conclusions

1. Lp (a)-apheresis as developed from Prokovski at the National Academy of Medical Sciences at Moscow allows for the most efficient elimination with a decrease of at least 80% of the pre-treatment Lp (a) level. However, due to the contents of apoprotein B Lp (a)-apheresis also eliminates LDL-cholesterol to some extent.
2. LDL-apheresis (immune apheresis) and liposorption appear to have a capacity of lowering about 76% of the initial value in patients with both FH and elevated Lp (a).
3. Filtration using the Kuraray LA 4 filter (in combination with centrifugal primary separation) allows for a decrease of 70% whereas whole blood adsorption is limited to a decrease of only 65%. However, it has to be taken into consideration, that plasma differential filtration is only semi-selective, removing other high molecular plasma components (e.g. fibrinogen about 65% and

total protein about 20% of the pre-treatment value) together with Lp (a) and that the extent of treatment is limited from the loss of fibrinogen.
4. The decrease of Lp (a) correlates with the plasma volume processed.
5. As Lp (a) immune-apheresis uses repetitive cycling it allows for processing virtually indefinite volumes and due to the re-use it is most economic. Thus, it can be recommended for the treatment of Lp (a) values exceeding 80 mg/dl.
6. A controlled trial applying Lp (a)-apheresis to patients with Lp (a) values of more than 80 mg /dl is most desirable, as the data available so far strongly support the usefulness of extracorporeal Lp (a) lowering therapy in patients with selectively elevated Lp (a), whereas an improvement of the currently available technologies appears to be necessary for patients with familial hypercholesterolaemia (especially homozygous patients) and simultaneous Lp (a) levels beyond 100 mg/dl.

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