Looking for new prognostic indices in liver transplantation. Considerations regarding a research project

Buscando novos índices prognósticos no transplante de fígado. Considerações a respeito de um projeto de pesquisa

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This year we published a paper concerning liver transplantation[1] with the objective of determining the postoperative levels of classical or pure model for end-stage liver disease (MELD), and changes in lactate or base excess levels as possible predictive factors of the type of outcome for patients submitted to orthotopic liver trasplantation (OLT). This investigation motivated other studies focused on the search for sensitive predictive indices specific for the type of outcome of invariably critically ill patients submitted to the most complex surgical procedure currently performed in human beings. We intend to present here four comments that we consider pertinent with the major objective of emphasizing important aspects of the topic under study.

1. Classical and pure MELD. The MELD formula does not fit all patients who are candidates for OLT

First of all it is important to remember that the MELD is nothing more than a score used worldwide to estimate the degree of systemic involvement in patients with end-stage liver disease. The score is based on some variables such as creatinine, INR and total bilirubin and permits to classify the patients by means of a point system according to the severity of their disease. It is on the basis of the MELD score that patients who are candidates for a liver transplant are assigned to the waiting list in such a way that the more critically ill ones will receive priority.

$$MELD = 0.957 \times \text{Log}_e(\text{Creatinine}^*) + 0.378 \times \text{Log}_e(\text{Bilirubin}^*) + 1.12 \times \text{Log}_e(\text{INR}) + 0.643$$

* Creatinine and Bilirubin are expressed in mg/dL.

Figure 1: MELD formula: Model for end-stage liver disease

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In our study, we consider the classical MELD and pure MELD as synonyms, and stating that MELD is "pure" was based on the principle that no arbitrary scoring was added to it, as done in so-called special situations not contemplated by the classical MELD. Indeed, in our studies based on prognostic indices we sought to attach a new variable to the MELD in order to improve it and make it more precise. Thus, the classical, already known, MELD or the pure MELD as we called it in our study, by receiving a new variable, would become more elaborate and specific. This was only our way to differentiate the MELD popularly known in the area from the MELD that we tried to create in our studies.

And this search also deals with the fact that the MELD does not fit all patients in the same way. What occurs is that the model does not contemplate all the needs for organ allocation and cannot be used in patients with hepatocellular carcinoma (HCC), familial amyloid polyneuropathy (FAP), and metabolic diseases, among others. What occurs in these patients is that the indicators that make up the MELD formula (INR, creatinine and total bilirubin) remain unchanged on a short-term basis, masking the real condition of the patient by assigning lower scores to him that do not reflect the severity of his situation. If we consider the use of the MELD as a prognostic postoperative index - the central topic of our study - we can see that it is even more inefficient since it does not contain in its formula indicators with the ability to discriminate between patients who will suffer complications and patients who will immediately obtain a good postoperative course.

On this basis, it is common to question the fact that the MELD is used as a key element in the clinical course of patients with liver disease, although it continues to be a mathematical formula that provides an objective value for the subjective clinical assessment of the degree of systemic involvement, indicating to the specialists a more exact direction of the course of the disease and greatly facilitating the decisions about the conducts to be followed.

Many studies have been published during the last few years proposing to improve the MELD as a formula for organ allocation and also as a prognostic postoperative index. Along this line, we started our search for new indicators, two of which proved to be relevant in the study mentioned above: base excess and serum lactate.

2. Base excess in medical practice

During liver transplantation, which is a situation of stress, ischemia and hypermetabolism, serum lactate levels increase due to the fall in hepatic function for their clearance from the organism caused by liver hypoxia and hypoperfusion.

In addition, at this time lactate production is increased, since lactate is the final product of glucose utilization during anaerobiosis. This reaction, in turn, occurs with release of hydrogen ions that acidify the medium and cause a fall in blood pH (metabolic acidosis). The return of pH to normal values occurs through the maintenance of acid-base equilibrium, which is mainly sustained by base consumption in order to reach homeostasis. Thus, we talk about base excess as an index that estimates the quantity of bases necessary for the restoration of physiological pH. With the increase in H+ ions during anaerobiosis, base consumption continues to increase, causing base equilibrium to become increasingly negative

3. Joint analysis of postoperative MELD, base excess and blood lactate as an index of the type of postoperative evolution of patients submitted to orthotopic liver transplantation

The results were expected, since we do know that ischemia and reperfusion injury alters the function of the organ and impairs lactate clearance. What we did not know was at what specific time the lactate and base excess values would provide safe clues regarding the prognosis of the patients.

What we saw with the study was that, a little after liver reperfusion, the patients who showed a favorable immediate postoperative outcome had lower lactate and base excess values than those who died and that, in addition, this difference continued to be present until the end of the procedure.

For an explanation, it is sufficient to return to the previous item, which shows that lactate and base excess are intimately related and are part of the physiological mechanism of homeostasis in stress situations.

4. The findings of the present study and their use to guide the management of patients submitted to OLT during the postoperative period

The importance of this result is based on the fact that, with the combination of these three parameters, we can better direct the postoperative care of more seriously ill patients. On this basis, we can perform a more expanded, constant and objective monitoring of their status after the transplant procedure. However, this was one of the first studies conducted by our group in the search for new prognostic indices.

We are currently involved in intensive and multidisciplinary work that counts with the collaboration of the Illinois Institute of Technology in the US, and is developing new ways of calculating the MELD[2]. What we are studying is the incorporation in two different ways of the lactate variable into the classical MELD by means of two equations. Both equations were obtained through regression analysis using patients data as independent variables and Boolean information as a dependent variable.

The difference between the two equations is that we used the logarithm of bilirubin, INR, creatinine and blood lactate as independent variables for the regression analysis of the first equation and only the MELD value and the logarithm of blood lactate for the regression analysis of the second equation, an important step that expresses the acute alteration of hepatic function.

This study has shown positive and more sensitive and specific results compared to the MELD, known and diffuse worldwide in the area of hepatology.

Referências

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