

Determinant factors in an expressive increasing of liver transplant in a single center

Fatores determinantes no expressivo aumento de transplantes de fígado em um único centro

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RESUMO: INTRODUÇÃO: O Hospital das Clínicas da Universidade de São Paulo é o maior hospital do Brasil. Seu programa de transplante foi o pioneiro neste país e realizou seu primeiro transplante de fígado em 1968. A lista de espera para transplante de fígado tem cerca de 700 pacientes, e ultrapassou mil há alguns anos. Apesar deste fato, nosso número de transplantes de fígado não era muito elevado (cerca de 50/ano) e tínhamos, como esperado, alta mortalidade na lista de espera. Este ano aumentamos significativamente o número de transplantes de fígado, atingindo 3 vezes a média dos últimos anos. OBJETIVO: Nosso objetivo é explicitar os fatores determinantes neste aumento expressivo do número de transplantes de fígado em um único centro no Brasil. MÉTODOS: Analisamos o número de transplantes de fígado no mesmo período do ano (de janeiro a setembro) em 2008 e 2009 no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. Foram avaliadas as razões deste aumento de transplantes de fígado em 2009 neste centro. RESULTADOS: Comparando o período de janeiro a setembro de 2008 com o mesmo período de 2009, o número de transplantes de fígado aumentou em 200% (35 para 105). A imprensa, o sistema de saúde pública, a organização da equipe transplantadora, a internação de pacientes críticos, o preparo pré-operatório, a aceitação de doadores com critérios expandidos, o programa de doadores vivos, e os fígados bipartidos foram determinantes neste aumento de transplantes de fígado nesta instituição. A sobrevida atuarial melhorou com o aumento do número de transplantes (75% para 85%). CONCLUSÃO: Ainda é possível aumentar o número de transplantes de fígado em países em desenvolvimento. O mecanismo desta transformação é multifatorial e necessita de esforço do governo, institucional e multidisciplinar. Apesar do uso de fígados marginais e bipartidos, o aumento do número de transplantes está relacionado a melhor resultado.

DESCRIPTORES: Transplante de fígado. Doadores vivos. Doadores de tecidos. Hospitais de ensino.

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INTRODUCTION

In Brazil there are a plenty of patients in the waiting list for liver transplant. The distribution of transplant centers is not regular and most of them are located at Sao Paulo State. Although there are many transplant teams at Sao Paulo, patients come from all over the country to Sao Paulo for medical assistance turning the wait list very long and the MELD score required for liver allocation extremely high.

The Clinical Hospital of Sao Paulo University (HC-FMUSP), the biggest Brazilian hospital, has two teams for liver transplant, one for adults and other for children. The transplant program was the first one to be set in Brazil and performed its first liver transplant in 1968. The adult waiting list for liver transplant has about 700 patients nowadays, and it has had more than a thousand some years ago. Even though, our number of liver transplants was not so high (about 50 a year) and we had, as expected, high waiting list mortality.

This year we increased significantly our liver transplant number, rising in 3 times our past few years' average¹. We would like to highlight the determinant factors in this expressive increasing number of liver transplants in a single center in Brazil, the HC-FMUSP.

MASS MEDIA

It is remarkable how media is important in people lives and decisions. The choices are made regarding the information basis that comes from mass media. Television, radio, newspapers and internet produces the principal source of information and it has indeed a great influence in transplant organ donation².

Our best example happened in the end of October 2008 when a 15-y.o. girl was kidnapped by her boyfriend and kept arrested for 3 days. The media showed the whole negotiation between the police and the kidnaper, that was unsuccessful and the case ended with the death of the young girl. This case was massively showed by media and had a national repercussion. The young girl donated all organs and the recipients were showed and interviewed. The number of cadaveric liver donation in Sao Paulo, that was of 34.4 (\pm 5.36) per month in 9 months before, raised to 56 (\pm 2.83) per month in 2 months after the event (p = 0.004). The number of cadaveric liver transplant in Clinical Hospital at Sao Paulo University was 4 (\pm 1.41)/month and raised to 14 (\pm 2.83)/month (p < 0.001).

Some authors have already highlighted the

negative effect of mass media in organ transplant, with sensationalists programs, sometimes creating myths about organ donation³. However, this case illustrates the power of mass media in the general population opinion and options. Finally, the media exposure indeed increased our number of liver donations and liver transplants (Figure 1 and 2).

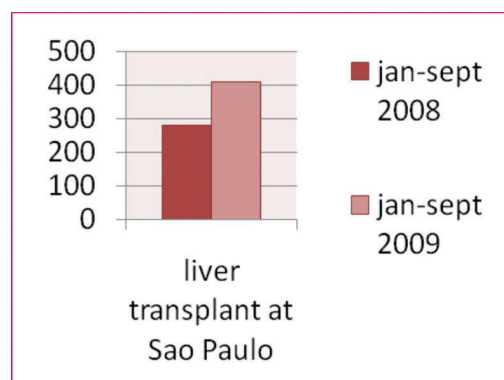


FIGURE 1. Number of liver transplant at Sao Paulo State from January to September 2008 (n=281) and from January to September 2009 (n=409), increasing 49%

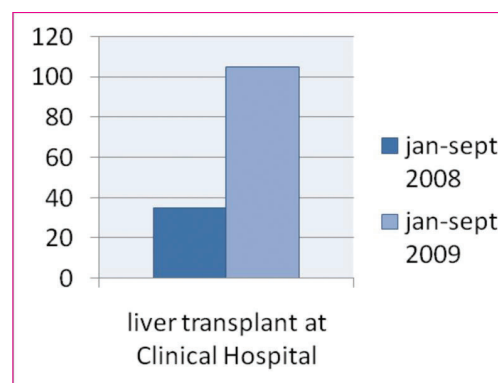


FIGURE 2. Number of liver transplant at Clinical Hospital of Sao Paulo Medical School from January to September 2008 (n=35) and from January to September 2009 (n=105), increasing 200%

PUBLIC HEALTH SYSTEM

The public health policy at Sao Paulo State is helping to increase the organ donation. Agents now are working in peripheral public hospitals specifically to find potential donors where there were many of them which were not notified to the Organ Procurement Organizations (OPOs). This active procurement and some instruction programs with health employees are certainly contributing in a solid gain in organ donation.

Although the event at the end of 2008 increased significantly the number of donations, similar events have happened before. At those circumstances, the average of organ donations raised right after the

event, but always falls only few months after the event. Differently, in this year occurred maintenance of a higher average in liver donation even several months after the mass media event, due to Sao Paulo health public policy and programs. The cooperation between donor hospitals and OPOs with aggressive strategies improved procurement performance. However, the actual situation is not a plateau, and the public service has to exhaust the possibilities to minimize the organ shortage. One potential alternative is the use of donors after cardiac death (DCD). Applying a mathematical model, Chaib *et al* analyzed the potential impact of using DCD at Sao Paulo State and found a relative reduction of 27% in waiting list⁴. Even in the United States, where the donation rate is about 23/million/year, the transplant and organ procurement institutions are doing a big effort to increase organ donation, with new strategies like 'DonorNet'⁵. In fact, the significant improvement in organ donation at Sao Paulo State was indeed a relevant factor in transplant volume expansion of Sao Paulo Clinical Hospital this year.

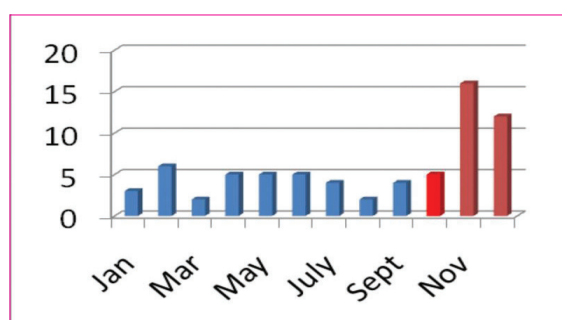


FIGURE 3. Number of liver transplant at Clinical Hospital of Sao Paulo in 2008 before and after an important media event in October 2008. $p < 0.001$ (data from Sao Paulo Public Health Division)

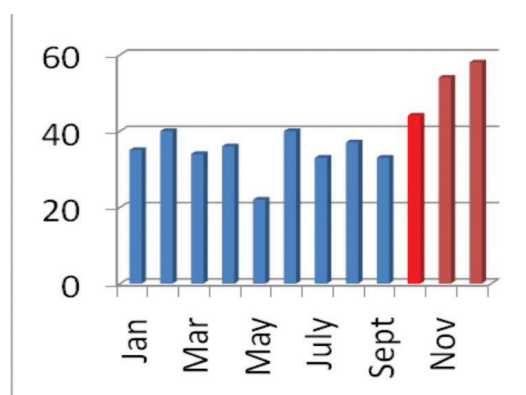


FIGURE 4. Number of liver donation in Sao Paulo State in 2008 before and after an important media event in October 2008. $p = 0.004$ (data from Sao Paulo Public Health Division)

TRANSPLANT TEAM

Our transplant team, with the same number of members than before, is now organized in order to perform two or three transplants at the same time or three or four transplants in sequence. Our structure with a second or third operating room, anesthesiologists, surgeons, intensivists, nurses, etc is now prepared for these concomitant surgeries and procedures.

The transplant team organization leads us to optimize transplant work and to accept two or three organs at the same time, what was impossible before.

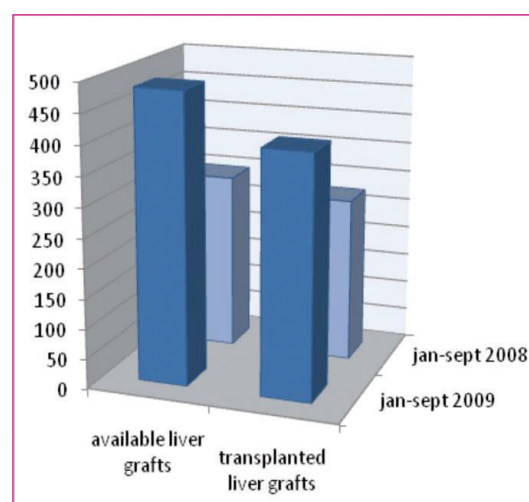


FIGURE 5. Number of available and transplanted liver grafts in Sao Paulo State from January to September of 2008 ($n = 298$ and 276) and 2009 ($n = 486$ and 405)

HOSPITALIZATION OF CRITICAL PATIENTS

There is a big problem in hospitalization of all critical patients in waiting list when it is needed. Many of them are hospitalized in small peripheral hospitals, where they are not appropriately treated, due to the lack of enough experience of these hospitals in treatment of such complicated patients. Moreover, these patients are extremely difficult to treat, with high morbidity and mortality, even in experienced centers.

In order to minimize this problem we raised our beds number in 20%, but, mainly, we tried to give priority to patients with high MELD scores. With this policy we can keep them alive or ameliorate a little for some days or weeks until the liver transplant. It seems an obvious issue, but when you have a long waiting list and so high MELD score which allowed you to transplant only above 29, you can have many complicated patients, with MELD between 18 and 25

for example, that died before achieving MELD score higher than 26. An ideal system would give a support to all patients in waiting list and transplant as soon as possible those with MELD greater than 20.

Our aim is to double our beds in a short period of time, and to expand even more the transplant number in attempt to offer a better backup to our waiting list patients and also decrease the level of transplantable MELD score.

PREOPERATIVE PREPARE

Patients waiting for liver transplant need many preoperative exams and specialist evaluations in order to identify comorbidities. Cirrhotic patients, even asymptomatic, may present heart or pulmonary diseases related to liver dysfunction. Such problems can complicate surgery or even turn it unfeasible. In the majority of transplant centers worldwide the preoperative evaluation is not a problem and it is easily and rapidly solved. However, in Brazil, the public institutions have a problem of high volume of patients that need specialist evaluations and image exams in comparison with its capacity. This situation results in patients in waiting list for liver transplant with a high MELD score that are not active in list because of incomplete preoperative evaluation.

The strategy was to make a big effort to optimize preoperative evaluations and exams in favor of high MELD score patients and let them rapidly prepared. Consequently our program obtained a larger number of transplantable patients. In another point of view, our patients should not be punished because of an institutional problem, nonetheless this is a national public health issue and we are a small part of it, however we achieved a better situation.

In practice this policy results in a higher volume of liver transplants in our institution.

ACCEPTANCE OF EXPANDED CRITERIA DONORS

On an intention to treat basis, we started to accept more widely expanded criteria donors. A marginal graft can be defined as an organ with an increased risk for liver failure or dysfunction. There are many variables that increase the risk of primary non function or dysfunction: steatosis, age, hypernatraemia, hemodynamic instability, infection, many days in intensive care unit, alcohol abuse, abnormal liver enzymes and some other factors. The population is becoming older all over the world, and it is hard to say if we have one liver without any of the mentioned factors. Many authors have described primary dysfunction and worse outcome related with

marginal livers⁶⁻⁸. On the other hand, some centers have been using marginal grafts with acceptable results and decreasing the waiting time for liver transplantation⁹⁻¹¹. In fact, with PELD score the best livers goes to children and it is not questionable. Moreover, in a developing country such as Brazil, peripheral hospitals are not well equipped, intensive care units are always full, and donors sometimes stays in urgency rooms. In summary, we are forced to accept marginal grafts to perform liver transplant. Feng et al have developed a 'donor risk index' according to factors that increase the likelihood of liver dysfunction¹². Schaubel et al showed a transplant survival benefit with MELD more than 15 even in high donor risk index¹³.

Hence our policy now is to analyze directly in all livers, independently of the laboratorial exams, and perform a biopsy when there is a doubt. We are using steatotic livers until 60%, and we are trying to reduce our cold ischemic time, especially in marginal livers and in recipients with high MELD score, in other words, in all cases.

LIVING DONOR PROGRAM

The living donor liver transplantation (LDLT) is already established in our service. On the other hand, adult to adult living transplants has been questioned in westerner countries, due to donor morbidity and mortality rates¹⁴ and the possibility of cadaveric transplants. However, LDLT is associated with reduced waiting list mortality and the results are equivalent to deceased donor liver transplantation (DDLT)^{15,16}.

The first LDLT was performed in this institution in 1988¹⁷. Since then the program of LDLT has expanded but mainly for children. The institution had a program for adult living donor transplant but stop for a while some years ago. In Brazil the rate of liver donors per million per year is about 7, much less than European countries and the United States. The fact explains our big waiting list and forces us to search alternatives for organ shortage. In fact we are in an intermediate position between Asia and Europe/USA in terms of donation, and this justifies an investment in an adult LDLT program.

We restarted our adult LDLT program and we operated 5 cases this year. The intention is to do it regularly once a week this year, and move to twice a week in a near future. Five cases is less than 5% of all our transplants this year, but we think that all measures together are making the difference. Moreover, we intend to reach more than 20% of our cases with LDLT, hence LDLT will certainly contribute to diminish mortality in waiting list.

SPLIT LIVER

Split liver is a great alternative to expand liver grafts. With established rules and trained teams, this technique doubles, with good results, the availability of organs. The problem of a separated adult liver transplant program is that almost all splittable livers go to children, and we are dependent on a children transplant program offer. In adult/adult split, a good organ is needed and we have to find a small recipient to match with a left liver. These facts turn the adult split complicated and difficult. Furthermore, in Brazil, the

center that performs the split doesn't interfere about allocation; the organ goes to the pool for distribution, another reason for loss of interest.

This year we performed 4 split liver transplant, 3 offered by children groups and 1 adult/adult split in which we divided the middle hepatic vein (Figure 6). We accepted all splited liver offered by children groups and now we are trying to prepare small recipients in order to let them ready for receiving a left lobe. The idea is to increase as much as possible split liver procedure, working together with children groups and doing liver split for adults.

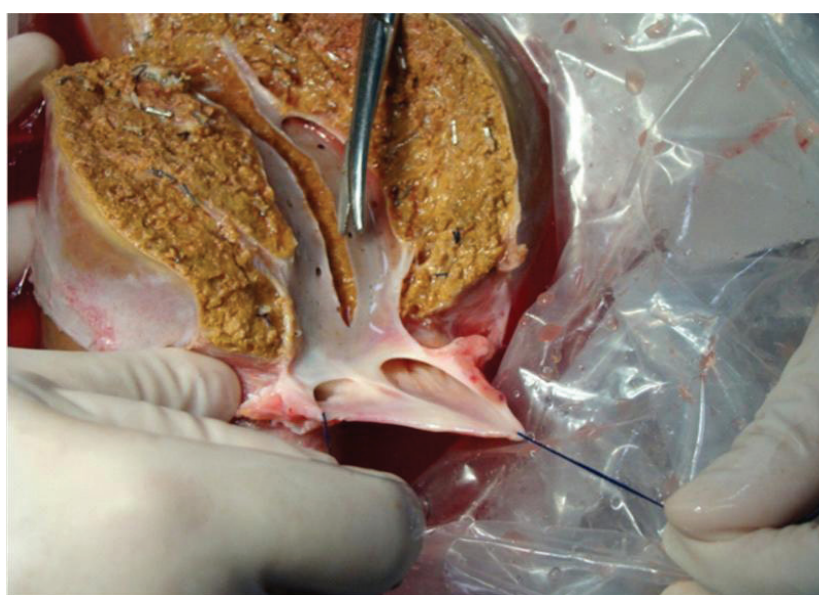


FIGURE 6. A adult/adult split liver with media hepatic vein divided

SURVIVAL AFTER THE TRANSPLANT INCREASING

Using all these measures to expand graft pool can cause technical challenges (split liver, living donors) and worse outcome and survival (marginal grafts, too sick patients). On the other hand with, a bigger volume it is possible to have a more prepared structure like intensive care units and surgical rooms, more experienced teams, in addition, it is possible to reduce transplantable MELD score, all of these contributing to a better result. It is difficult to say what is the consequence of this policy in outcome, but definitely the mortality in waiting list is diminished by it.

Actually our survival rate improved with the increased number of transplants (Figures 7 and 8). The reasons listed above can explain it. In addition to lower waiting list mortality, a better survival rates get an excellent intention to treat strategy.

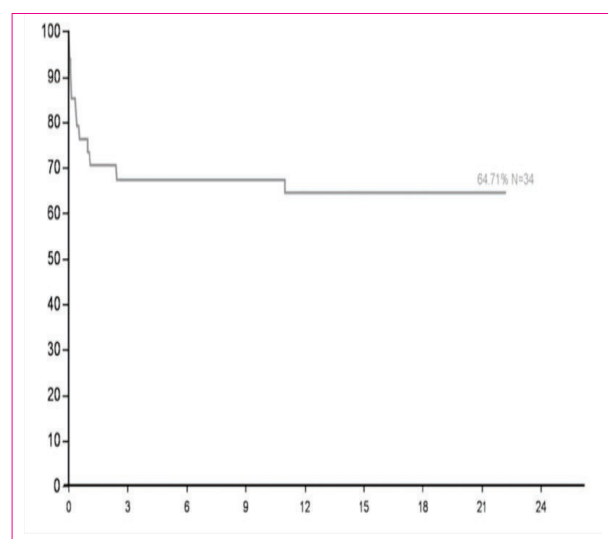


FIGURE 7. Survival rate of cadaveric liver donor transplants from January to September 2008 at Clinical Hospital of Sao Paulo

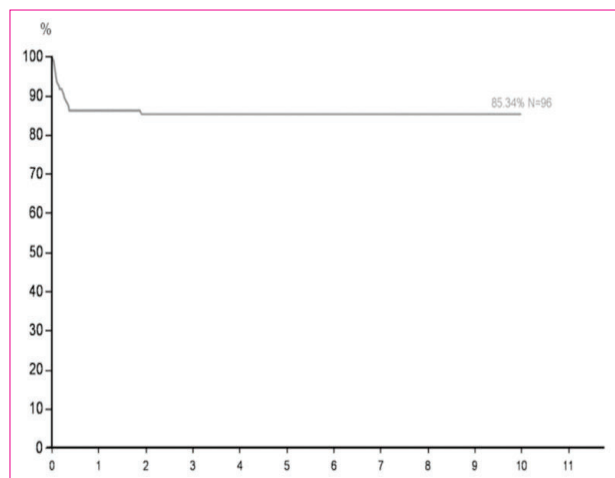


FIGURE 8. Survival rate of cadaveric liver donor transplants from January to September 2009 at Clinical Hospital of Sao Paulo.

DISCUSSION

The rationale of these measures is both to

maximize the organ utility and to reduce the mortality of those on the waiting list. Our unit has embraced the possible changes necessary to increase the volume of cases, but not at the expense of quality in outcomes. Actually, the quality has increased with the volume, which explains the better survival rate besides the use of marginal organs and split livers.

It is known that in developed countries, experienced centers have already exhausted almost all these measures, and they are looking for other options to solve the big problem of organ shortage. This paper illustrates that in developing countries we have a great potential, with regional differences from country to country of course, but that can be explored in order to improve our cirrhotic patients care and the final treatment with liver transplant.

In conclusion, It is still possible to increase the number of liver transplants in developing countries. The mechanism of such change is multifactorial and it needs government, institutional and multidisciplinary efforts. Besides the use of marginal and split livers, the increasing rate of transplants is related to better outcome.

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ABSTRACTS: **INTRODUCTION:** The Clinical Hospital of Sao Paulo University is the biggest hospital of Brazil. Its transplant program was the pioneer in this country and it performed its first liver transplant in 1968. The adult waiting list for liver transplant has about 700 patients nowadays, and it has had more than a thousand some years ago. Even though, our number of liver transplants was not so high (about 50 a year) and we had, as expected, high waiting list mortality. This year we raised significantly our liver transplant number, increasing in 3 times our past few years' average. **AIM:** We would like to highlight the determinant factors in this expressive increasing number of liver transplants in a single center in Brazil. **METHODS:** We analyzed the number of liver transplants in the same period of the year (from January to September) in 2008 and 2009 at the Clinical Hospital of Sao Paulo University Medical School. It was evaluated the reasons of the increasing rate of liver transplants in 2009 at this center. **RESULTS:** Comparing the period from January to September 2008 with the same period of 2009, the liver transplant number increased 200% (35 to 105). Mass media, public health system policy, transplant team organization, hospitalization of critical patients, preoperative prepare, acceptance of expanded criteria donors, living donor program, and split livers were determinant in this raising of liver transplants at this institution. The actuarial survival rate improved with the increasing number of liver transplants (75% to 85%). **CONCLUSION:** It is still possible to increase the number of liver transplants in developing countries. The mechanism of such change is multifactorial and it needs government, institutional and multidisciplinary efforts. Besides the use of marginal and split livers, the increasing rate of transplants is related to better outcome.

KEY WORDS: Liver transplantation. Living donors. Tissue donors. Hospitals, teaching.

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