Is it Necessary to Suspend Betablockers in Decompensated Heart Failure with Low Output?

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Abstract

Background: There is evidence that the suspension of betablockers (BB) in decompensated heart failure may increase mortality. Dobutamine (dobuta) is the most commonly used inotrope in decompensation, however, BB and dobuta act with the same receptor with antagonist actions, and concurrent use of both drugs could hinder compensation.

Objective: To evaluate whether the maintenance of BB associated with dobuta difficults cardiac compensation.

Methods: We studied 44 patients with LVEF <45% and the need for inotropics. Divided into three groups according to the use of BB. Group A (n=8): those who were not using BB at baseline; Group B (n=25): those who used BB, but was suspended to start dobuta; Group C (n = 11): those who used BB concomitant to dobuta. To compare groups, we used the Student t, Fisher exact and chi-square tests. Considered significant if p < 0.05.

Results: Mean LVEF 23.8 ± 6.6%. The average use of dobuta use was similar in all groups (p = 0.35), and concomitant use of dobutamine with BB did not increase the length of stay (BB 20.36 ± 11.04 days vs without BB 28.37 ± 12.76 days, p = NS). In the high dose, BB was higher in patients whose medication was not suspended (35.8 ± 16.8 mg/day vs 23.0 ± 16.7 mg/day, p = 0.004).

Conclusion: Maintaining BB associated with dobutamine did not increase the length of hospitalization and was not associated with the worst outcome. Patients who did not suspend BB were discharged with higher doses of the drug.

Key words: Heart failure; decompensated heart failure; dobutamine/administration & dosage; low cardiac output.

Introduction

Heart failure is a prevalent disease, and patients have decreased quality of life and live with high risk of life. Epidemiological studies have shown that patients with HF are hospitalized very frequently and that mortality is higher than many cancer types.

The modern treatment with neurohormonal blockers is modifying the natural morbid history, reducing symptoms, improving quality of life and reducing the high morbimortality. Among neurohormonal blockers, betablockers have an important role by modifying more intensely morbimortality related to disease.

Since the documentation of its efficacy, the prescription of BB in HF has been growing. At first it was just prescribed for fear of negative inotropic effect, but grew with the release of successive clinical trials proving its efficacy and safety. At InCor, it was possible to document such an increase. In 1999, 9.5% of outpatient received prescription of betablockers against 77.2% in the year 2004.

Although properly treated, the variable percentage of patients with HF decompenses. It was found an increase of patients treated with betablockers and, consequently, an increase of patients who decompensate during treatment. In view of the concept that BB has negative inotropic effect, these are suspended in cardiac decompensation by most doctors. However, retrospective analysis of clinical trials and registries of patients with HF have been documenting the evolution of patients in whom BB was suspended is accompanied by higher mortality than the one observed when BB is kept.

The controversy over maintaining or suspending BB in cardiac decompensation, adds to the doubt of how to treat it, especially in patients with low cardiac output table in decompensation. Dobutamine, when necessary, is the most used medication for inotropic support. Whereasdobutamine is an inotropic beta stimulant and that betablockers block the beta adrenergic receptors, the prescription of the two concurrently may result in reduced inotropic effect of...
dobutamine, as well as difficult and prolong the time required to obtain treatment for cardiac compensation.

In our hospital, we have seen an increasing number of patients using concomitant betablocker and dobutamine. Thus, we analyzed prospectively if the evolution of patients using concomitantly the two drugs would be different from those without betablocker decompensation or those in which the betablocker was suspended for prescribing inotropic support with dobutamine.

**Methods**

We analyzed prospectively, by means of a cohort study, 44 patients in functional class IV, hospitalized for compensation of heart failure in the period from February to December 2005. We selected patients older than 18 years, with a left ventricle ejection fraction below 45% and use of dobutamine. The study excluded patients with cardiac pacemakers. All patients were evaluated clinically and underwent laboratory tests that included complete blood test, urea, creatinine, sodium and potassium content. To characterize the patients as per the degree of cardiac impairment, it was considered the echocardiogram performed prior to hospitalization, if the examination had been conducted within the previous six months before admission. It not, the echocardiogram was performed at admission. These patients with decompensated HF, eight (18.18%) were not taking betablockers, and 36 (81.81%) were. When dobutamine was prescribed, the betablocker was discontinued in 25 (69.44%) patients and maintained in 11 (30.55%) cases. To analyze the data, patients were divided into three groups according to the use of betablockers: Group A (n = 8) - who were not using BB at baseline, Group B (n = 25) - who used BB, but was suspended to start dobutamine, Group C (n = 11) - who used the BB concomitant with dobutamine.

Patients were followed up during hospitalization, analyzing the days needed for compensation, the time it was necessary to keep the dose of carvedilol and dobutamine in which the patient was discharged. The three groups were compared regarding clinical features, as to the time of use of inotropic and length of hospitalization.

Continuous variables were presented by mean ± standard deviation and categorical variables as percentages. The t test was used for comparison among the groups. The presented P values are two-tailed, and a significance level of < 0.05 was adopted.

**Results**

Table 1 shows the main characteristics of the studied patients. Most patients were male, with a significant reduction in ejection fraction, large LV dilation and levels of urea and creatinine slightly elevated. The hospitalization was prolonged, and patients were discharged with higher doses of carvedilol than in the admission. Eighty-one percent of patients with decompensated HF were using BB.

Table 2 shows the characteristics of patients according to the groups. There was no difference between them in age, ejection fraction, hemoglobin, sodium and potassium levels.

The patients of the group hospitalized without betablocker (Group A) had levels of urea and creatinine lower than those that decompensated and were taking betablockers (Groups B and C). Patients in Group C where the betablocker was kept is discussed in the text.
maintained during treatment for cardiac failure had greater ventricular enlargement.

The hospitalization was similar in all three groups, but patients who were not taking betablockers on admission (Group A) needed inotropic for longer periods than patients who were taking betablockers on arrival to the Emergency Room (Tables 2 and 3). The dose of carvedilol at discharge in Group C was higher than that of the group in which carvedilol was suspended for the introduction of inotropic and than that group that was taking it at the time of admission.

Discussion

The natural history of heart failure, a disease with features of malignancy, has been modified with modern treatment. Betablockers, through the reversal of cardiac remodeling, improve the quality of life, are important in reducing mortality and have been identified as the main drug for controlling HF.

If there is doubt about the value of betablockers in the treatment of chronic HF, the same does not occur when the patient decompensates. With the increasing number of patients using betablockers, the number of cases with cardiac decompensation also increases in the presence of optimized treatment and using beta blockers. In this situation, should betablocker be discontinued, or can it be maintained? In our institution, based on the result of studies suggesting that betablocker discontinuation or even reduction could be accompanied by increased mortality, the non suspension of the drug routinely started in all cardiac decompensation conditions. Here we present the results of the analysis of patients hospitalized for cardiac compensation in 2005 who had or not betablocker suspension during cardiac compensation.

Patients with HF who did not compensate or not improved with treatment administered in the Emergency Room of Instituto do Coração were hospitalized in our institution, with the selection of the most severe patients. This sample was consisted of patients in functional class IV signs of pulmonary and systemic congestion and signs of low cardiac output. In the Emergency Room, everyone had a prescription of dobutamine in the face of the presence of low output and were hospitalized to complete the cardiac compensation rate. From the 44 patients with decompensated heart failure, eight (18.18%) were not taking betablockers, and 36 (81.81%) were. When dobutamine was prescribed, the betablocker was discontinued in 25 (69.44%) and maintained in 11 (30.55%) patients.

We sought, in this study, to determine whether the clinical evolution during hospitalization was different whether or not keeping the betablocker and whether or not the combination of dobutamine with betablockers might interfere in this evolution.

The first point that deserves mention is the fact that most patients with decompenation and went to the Emergency Room was in use of betablockers (81.8%). That number matches the survey conducted at our institution, which revealed that over 70% of patients with HF to receive outpatient prescription of BB.

The population studied in our hospital is very serious and generally requires several days of hospitalization to compensate (average of 23 days). The hospitalization time is longer than that reported in other studies. It is described that, in general, patients are hospitalized for four to five days to compensate, when the HF condition is not severe, and around nine days for the most severe ones. In Rio de Janeiro, for patients treated at the Emergency Room of a private institution, length of hospital stay was 9.5 days, and in Porto Alegre in a school hospital like ours, it was of 11 days, both times smaller than ours. The highest severity of our cases may explain, in part, that long hospitalization time. We have no data to stratify the severity of HF in Brazilian hospitals.

In a previous study, we compared the profile of our patients with those described in American ADHERE registry. Dividing our cases according to the stratification of ADHERE study and comparing the two cohorts, we observe that our population is generally more severe than that which participated in ADHERE registry, because 74.9% of patients hospitalized in our hospital with systolic pressure below 115 mmHg, while in ADHERE registry only 18.5% were hypertensives. Thus, our greatest severity is one of the explanation for longer periods of hospitalization and need for inotropic.

In the analysis of hospitalization time, it was observed that patients who were not using betablockers to decompensate were hospitalized longer (28.37 ± 12.76 days) and received dobutamine for a longer time (15.37 ± 4.45 days) than the other two groups. The average length of hospitalization was 24% higher in patients in Group A than in patients who were being treated with betablockers, which was subsequently suspended, and 39% higher than for the group in which the betablocker was maintained. Concerning the time of inotropic, and decompensation in patients who were not in use of BB was 82% higher than in Group B and almost the double than in Group C (94%). The differences did not reach statistical significance, but the absolute numerical difference was

Table 3 - p values in comparison among groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>A vs B</th>
<th>A vs C</th>
<th>B vs C</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.4858</td>
<td>0.6274</td>
<td>0.9728</td>
</tr>
<tr>
<td>Gender</td>
<td>0.6268</td>
<td>0.5061</td>
<td>0.4562</td>
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<tr>
<td>LVEF*</td>
<td>0.8284</td>
<td>0.8028</td>
<td>0.7545</td>
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<td>LVDD</td>
<td>0.5778</td>
<td>0.3529</td>
<td>0.1093</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.3158</td>
<td>0.1803</td>
<td>0.5956</td>
</tr>
<tr>
<td>Urea</td>
<td>0.0020</td>
<td>0.0996</td>
<td>0.4314</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.0016</td>
<td>0.0027</td>
<td>0.1533</td>
</tr>
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<td>Sodium</td>
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<td>0.7792</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.2664</td>
<td>0.0524</td>
<td>0.1209</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0.3476</td>
<td>0.2207</td>
<td>0.5416</td>
</tr>
<tr>
<td>Inotropic</td>
<td>0.1235</td>
<td>0.1180</td>
<td>0.8053</td>
</tr>
<tr>
<td>BB* pre</td>
<td>NA</td>
<td>NA</td>
<td>0.4145</td>
</tr>
<tr>
<td>BB discharge</td>
<td>0.5910</td>
<td>0.2405</td>
<td>0.0531</td>
</tr>
</tbody>
</table>

*LV - left ventricle; **BB - betablocker (carvedilol).
great. It is interesting to note that the group was not receiving betablocker on arrival at the Emergency Room had urea and creatinine levels lower than the group that was in use of BB. Not using the BB does not seem to have occurred because these patients had more severe or worst HF conditions.

Our results showed that the use of the betablockers to decompensate do not indicate that compensation will be more difficult. Patients treated with betablockers needed less time of inotropic for the compensation and were, overall, less time in hospital than those without betablocker (20.36 ± 11.04 days and 22.80 ± 10.31 days vs 28.37 ± 12.76 days). This finding can be inferred that using betablockers to decompensate does not identify a more severe group or a group in which the cardiac compensation will be more difficult. There was no difference in the prescription of diuretics or vasodilators for compensation in the three groups.

When comparing the groups in which the betablocker was discontinued when starting the infusion of dobutamine with the group in which the betablocker was maintained throughout the infusion, there was no significant difference between them. As for time of use of inotropic, and the total length of hospital stay, although the absolute numbers have been lower in the group where the betablocker was maintained, there was no statistical significance (Tables 2 and 3). This finding suggests that the non-suspension of betablockers did not influence negatively the outcome of cases.

Undoubtedly it contributes to prolonged hospitalization, the conduct of introducing and optimizing the dose of betablocker during hospitalization. When analyzing the three groups, we observed that the patients remained hospitalized for about 13 days after discontinuation of inotropic. If we reduce those 13 days from the total hospitalization time, we can verify that the remaining time does not differ from those described in the Brazilian hospitals.

However, with this conduct, it was possible to discharge patients with effective dose of carvedilol. The mean dose of the high one was 26.84 ± 17.14 mg/day, i.e., on average, 12.5 mg twice a day. Comparing the three groups, we found that the dose of Group C, where the betablocker was not suspended during the use of dobutamine and cardiac compensation was significantly higher than the other two groups, those who were hospitalized without prescription of betablocker and those in which the drug was discontinued. The dose of group C was 34% higher than the group who were not taking betablockers in the Emergency Room and 55% higher than in the carvedilol group that was suspended by the introduction of dobutamine (35.79 ± 17.25 mg/day vs 26.56 ± 18.83 mg/day and 23.00 ± 16.08 mg/day).

In the literature, there are more and more articles documenting that the non suspension of betablockers in cardiac decompensation is accompanied by improved outcome. The first one was the article by Metra et al which, based on data from the COMET study, found a mortality reduction of 59% for patients who had dose maintained in respect of those whose dose was reduced or suspended. Interestingly, in the COMET study, 8% had discontinued betablocker, and 22%, a reduction of the dose and the dose maintained at 70% of cases. Without doubt, the form of presentation of decompensation may be considered. In such cases, almost the totality did not present low output condition such as ours, but the important thing is that only 30% of patients had their dosage reduced or discontinued, a finding that indicates that it is possible to keep the BB in cardiac decompensation and that most of them had a good evolution without suspension. In this study, the hospital stays of patients who had discontinued betablockers was of 27 ± 53 days. Those in which the betablocker dose was reduced, 11 ± 9 days, and, where they had kept the betablocker dose during decompensation, 9 ± 8 days.

Orso et al in the Italian registry documented that the non-use of betablockers or suspension in patient hospitalization were associated with increased mortality, confirmed by multivariated analysis. It was identified that patients who were hospitalized without betablockers and did not receive during hospitalization had a risk of life 3.28 times higher than the group that was using BB and this was maintained. They also observed that for those using BB and suspended in the hospital, an increase of 4.20 times the risk of life occurred.

Fonarow et al in OPTIMIZE-HF program, found that 56.9% of patients were using betablockers at decompensation and that suspended it in only 3.3% of cases. At discharge, 26.6% began receiving the drug. They found that maintaining the betablocker was associated with reduced risk of death of 40% compared to those without betablocker. In contrast, the suspension of betablockers was associated with increased risk of death of 2.3 times than those who continued with the medication.

Jondeau et al recently published the study B-CONVINCED, much like ours, but with less severe patients. It prospectively analyzed 147 patients who were hospitalized with decompensated heart failure, an ejection fraction inferior to 40%, previously using betablockers. Patients were divided into two groups according to the maintenance dose of BB on admission or not. After three days of evolution, there was no difference between the groups regarding the compensation of heart failure. More importantly, there was no difference in BNP levels, re-hospitalization and mortality in three months. According to our study, patients in the B-CONVINCED that maintained BB during decompensation were using higher doses of medication three months after discharge (90% vs 76%)7.

These results provide the substrate for not routinely suspending BB when the patient decompensates. It is important to emphasize that in these studies, most patients showed no signs of low output and probably did not receive inotropic agents for compensation. Still, there was improvement in survival in the medium- and long-term and not during hospitalization. However, patients who are discharged from hospital using a higher dose of betablockers will also benefit in the medium- and long-term.

Our data extend this indication, showing that for patients with decompensated low output signals that require treatment with inotropic agents, it is also possible to keep the BB, but this conduct was not accompanied by greater difficulty in compensating patients. Moreover, the data suggest that patients responded well to conduct, requiring shorter hospitalization and inotropic time for compensation.
Not suspending BB facilitates optimization of treatment at discharge. Whereas many physicians are still afraid to prescribe it, and when they do, they use low doses, especially in patients with decompensation and required inotropic support for compensation, to discharge with optimal treatment is essential so that the patient may benefit from such treatment.

In the literature, there are several studies that show that starting the BB during hospitalization increases the rate of prescription, being this increase accompanied by better evolution\(^\text{18-20}\). Among these, we have the IMPACT study, which proved that the action of starting BB on admission was associated with a reduction of mortality\(^9\).

Following this line of research, Fowler et al\(^\text{20}\) identified that there is a huge number of patients not receiving BB in the correct dose, confirming that 55% are being treated with a dose lower than 25 mg twice a day, and 9% had their medication discontinued\(^\text{20}\). They found that about 30% of patients received no prescription of BB in the follow-up, and the non prescription had as main cause the non starting after hospitalization\(^\text{20}\).

These data point to the importance of starting treatment with BB during hospitalization. In our department, we extended this procedure by keeping the patient hospitalized for a few more days and seeking to discharge with optimal treatment, as it is observed a decrease in the rate of re-hospitalization and mortality and that this reduction is as great as the prescribed BB dose is high. With this procedure, we could optimize treatment for all, and most had a high dose of more than 12.5 mg of carvedilol twice a day (26.84 ± 17.24 mg/day).

With no suspension of BB on admission, the patients achieved with the optimization higher doses of BB (35.79 ± 17.25 mg/day).

In conclusion, it is possible to keep the BB during cardiac decompensation, even in patients with signs of low cardiac output requiring inotropic support. This conduct was not accompanied by the worst outcome. We could observe that dobutamine and BB associated can be used and that the evolution of these patients was similar to those in which the BB was suspended. By not suspending the BB, patients might be discharged with optimal doses of medication.

This approach may have an impact on survival, since the optimal treatment is accompanied by improved outcome. Undoubtedly, studies are needed with larger sample and in which patients are followed in order to confirm this hypothesis.

Study limitations
This is a non randomized, observational study. Although the difference between the groups is evident, it did not reach statistical significance probably due to sample size. Randomized studies are needed to clarify the issue.

Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Study Association
This study is not associated with any post-graduation program.

References


