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ORIGINAL ARTICLE

Initiation or maintenance of beta-blocker therapy in patients hospitalized for acute heart failure

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Abstract *Background* Beta-blockers have been recommended for patients with heart failure and reduced ejection fraction for their long-term benefits. However, the tolerance to betablockers in patients hospitalized with acute heart failure should be evaluated. *Objective* To estimate the proportion of patients hospitalized with acute heart failure who can tolerate these agents in clinical practice and compare the clinical outcomes of patients who can and cannot tolerate treatment with beta-blockers. *Setting* Two reference hospitals in cardiology. *Methods* Retrospective cohort study of consecutive patients hospitalized for acute heart failure between September 2008 and May 2012. Population-based sample. During the study period, 325 patients were admitted consecutively, including 194 individuals with an acute heart failure diagnosis and systolic left ventricular dysfunction and ejection fraction ≤45 %, who were candidates for the initiation or continuation of beta-blockers. *Main outcome measure* The percentage of patients intolerant to beta-blockers and the clinical characteristics of patients. *Results* On admission, 61.8 % of patients were already using beta-blockers, and 73.2 % were using beta-blockers on discharge. During hospitalization, 85 % of patients used these agents for some period. The main reasons for not using betablockers were low cardiac output syndrome (24.4 %), bradycardia (24.4 %), severe hypotension or shock (17.8 %), and chronic obstructive pulmonary disease (13.3 %). Patients who were intolerant or did not use a beta-blocker had a longer hospital stay (18.3 vs. 11.0 days; $p < .001$), greater use of vasoactive drugs (41.5 vs. 16.3 %; $p < .001$, CI 1.80–7.35), sepsis and septic shock (RR = 3.02; CI 95 % 1.59–5.75), and higher mortality rate during hospitalization (22.6 vs. 2.9 %; $p < .001$; CI 3.05–32.26). *Conclusion* Beta-blockers could be used in 73.2 % of patients hospitalized for acute heart failure. Patients who can not tolerate BB presented a higher frequency of adverse clinical outcomes including frequency of sepsis, use of vasoactive drugs, average length of hospitalization, and death.

Keywords Acute heart failure · Beta-blockers · Brazil

Impacts on practice

- Approximately 25 % of patients hospitalized with acute heart failure in Brazil can not tolerate the introduction of beta-blockers;
- The intolerance to beta-blockers in hospitalized patients can have a negative impact on clinical outcomes.

Introduction

The symptomatic treatment of acute heart failure (AHF) during hospitalization is mainly based on the introduction of diuretics and vasodilators [1–3]. Beta-blockers (BBs), though they do not improve symptoms, are recommended for the reduction of adverse clinical outcomes after discharge and should therefore be maintained or initiated with

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the aim for long-term treatment [1]. Previous studies have demonstrated evidence of the safety of BB maintenance therapy in patients with AHF who do not have hypotension, low output, bradycardia, or hypoxemia on admission and are already using this class of drugs [4]. By virtue of their perceived long-term benefit, clinical guidelines suggest that patients with heart failure with reduced ejection fraction (HFrEF) should be discharged from the hospital whenever possible using BBs [1, 2].

However, patients with more severe disease, including evidence of low cardiac output, possibility of imminent use of vasoactive amines, severe hypoxemia, or apparent volume overload, have not been considered for the early use of these agents in any randomized study. Moreover, previous studies have shown that BBs are related to a negative inotropic and chronotropic effect, lowering of blood pressure, and increase in plasma type B natriuretic peptide (BNP), which may be clinically relevant in unstable patients [5, 6]. These potential adverse effects of this drug class may be difficult to recognize due to their overlap with the natural course of AHF.

Aim of the study

The aim of the present study was to estimate the proportion of patients with AHF with systolic dysfunction of the left ventricle who tolerate BBs during hospitalization and compare the clinical outcomes of patients who can and cannot tolerate treatment with beta-blockers.

Ethical approval

The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the local Research Ethics Committee (resolution number 75/2011).

Methods

This retrospective cohort study included patients hospitalized for decompensated HFrEF at two reference centers in cardiology in Salvador, Bahia, Brazil. We retrospectively analyzed all data from patients who were hospitalized for decompensated HF from September 2008 to May 2012. Data were collected from electronic medical records, with standardized questionnaires completed by doctors and medical students.

Cases were defined as patients hospitalized with a diagnosis of HFrEF on admission (with ejection fraction of $\leq$40 % on transthoracic echocardiography). Inclusion criteria were a primary diagnosis of decompensated HFrEF and age over 18 years old. Patients whose hospital stay was <24 h due to death or hospital discharge, whose primary reason for admission was not confirmed as decompensated heart failure (such as those admitted for pacemaker implantation, cardiac catheterization, or elective surgeries), or with a life expectancy of <6 months were excluded.

The prescribed dose of BBs was defined according to the Brazilian Guidelines on AHF [7, 8], classified as a maximum dose of 100 % of the recommended dose, moderate dose of 50–99 % of the recommended dose, and minimum dose <50 % of the recommended dose, for the purpose of comparison between different BBs. Patients who did not receive this drug class from early admission, had their dose suspended during the course of hospitalization, or died or were discharged without using these agents were classified as intolerant or with contraindications to BBs use.

Acute renal failure was defined as an increase in serum creatinine level during hospitalization of $\geq$0.3 mg/dl and/or increase of $\geq$1.5 times the baseline [9]. Implantable devices were defined as pacemaker implantation, implantable cardioverter-defibrillator, and/or biventricular pacing.

The results were analyzed using descriptive statistics, with continuous variables expressed as mean, standard deviation, and median and compared using Student's t test for normal distributions and the Mann–Whitney test for nonparametric distributions. Categorical variables were analyzed according to the distribution of absolute and relative frequencies, with comparisons between proportions made with the Chi square test. A threshold for statistical significance of 5 % was used for all analyses.

Results

During the study period, 194 patients were included, involving 325 hospital admissions. The characteristics of all patients and those who tolerated (72.7 %) or did not tolerate (27.3 %) BBs are described in Table 1.

The majority of patients were male (60.3 %), elderly (median 63 years), and with the following risk factors in descending order: hypertension (67.5 %), diabetes (26.8 %), atrial fibrillation (25.7 %), and chronic kidney disease (19.6 %). The mean left ventricular ejection fraction and systolic blood pressure (SBP) were 31.1 % and 121 mmHg, respectively. The most frequent precipitant factor for decompensation was therapeutic non-adherence (26.3 %), and the most frequent etiologies were ischemic and Chagas heart disease (36 and 26.2 %, respectively). At the time of admission, 61.8 % (n = 120) of the patients reported using BBs, and at discharge, 72.7 % (n = 141) (Table 2). Moderate doses were achieved in 28.8 % (n = 56) of the patients, while 44.8 % (n = 87) used the minimum dose.

The main reasons for not using BBs (n = 53) were low cardiac output syndrome in 20.8 % of patients (n = 11), bradycardia in 20.8 % (n = 11), severe hypotension or shock in 15.1 % (n = 8), chronic obstructive pulmonary

Table 1 Baseline characteristics of patients according to tolerability to beta-blocker use

	All (n = 194)	*BB*-tolerant (n = 141)	*BB*-intolerant (n = 53)	*p* value
Patients (%)	100	**72.7**	**27.3**	**–**
Age—year				–
Mean	62.4 ± 13.4	62.2 ± 13.1	63.0 ± 14.3	.71
Median	63	63	65	–
Range	22–93	22–93	24–89	–
Male—no. (%)	117 (60.3)	89 (63.1)	28 (52.8)	.19
Hypertension—no. (%)	131 (67,5)	100 (71)	31 (58.5)	.03
Diabetes—no. (%)	52 (26.8)	38 (27)	14 (26.4)	.81
Atrial fibrillation—no. (%)	50 (25.7)	35 (24.8)	15 (28.3)	.77
Chronic kidney disease—no. (%)	38 (19.6)	21 (14.9)	17 (32)	.01
Systolic blood pressure—mmHg				
Mean	121 ± 28.2	123.9 ± 29.6	113.5 ± 22.6	.03†
Median	120	120	110	.03†
Range	80–230	80–230	80–190	–
LVEF, mean	31.1 ± 7.9	31 ± 8	31.5 ± 7.8	.66
Precipitant factors (%)				
Therapeutic non-adherence	51 (26.3)	37 (26.2)	14 (26.4)	.89
Infection	22 (11.3)	15 (10.6)	7 (13.2)	.73
Acute coronary syndrome	19 (9.8)	14 (9.9)	5 (9.4)	.80
Atrial fibrillation	11 (5.7)	7 (5)	4 (7.5)	.73
Other	20 (10.3)	14 (9.9)	6 (11.3)	.89
Heart failure etiology (%)				
Ischemic	70 (36)	52 (36.8)	18 (34)	.69
Chagas heart disease	51 (26.2)	35 (18)	16 (30.2)	.46
Hypertensive	18 (9.2)	14 (9.9)	4 (7.5)	.78
Valvular	10 (5.1)	6 (4.2)	4 (7.5)	.47
Other	9 (4.6)	7 (5)	2 (3.8)	.99

Data are expressed as relative frequency; numbers in parentheses indicate absolute numbers of individuals unless otherwise indicated

Chi-square test was used to compare qualitative variables. Quantitative continuous variables are expressed as mean ± SD when demonstrating a parametric distribution or median ± IQR, when demonstrating a non-parametric distribution pattern

LVEF left ventricular ejection fraction, *IQR* interquartile range, *SD* standard deviation

† Mann–Whitney test; * Pearson Chi square

Table 2 Usage profile of beta-blockers on admission, hospital stay, and discharge (n = 194)

	Admission	Hospital stay	Discharge
Frequency of use (%)	120 (61.8)	165 (85.0)	141 (72.7)
Dose reduction (%)[a]	21 (10.8)	16 (8.2)	–
Suspension of use (%)	12 (6.2)	24 (12.4)	–
Start of use (%)	31 (15.9)	24 (12.4)	–
Increase in the dose (%)[a]	28 (14.4)	29 (14.9)	–

[a] Increase or reduction of ≥50 % compared to baseline dose

disease in 11.3 % (n = 6), persistent pulmonary congestion in 7.5 % (n = 4), and an unidentified cause in 7.5 % (n = 4). BBs were used in conjunction with vasoactive amines during the same hospitalization period in 23.2 % (n = 45) of the patients. Patients who did not tolerate maintenance or initiation of BB therapy during hospitalization had a lower frequency of hypertension, lower mean SBP, and higher prevalence of chronic kidney disease.

In terms of clinical outcomes, patients who did not tolerate or did not use BBs had a higher mean length of hospitalization ($p < .001$), need for vasoactive amines (RR = 2.55; 95 % CI 1.56–4.16), incidence of sepsis (RR = 3.02; 95 % CI 1.59–5.75), and mortality rate (RR = 7.93; 95 % CI 2.67–23.49), as shown in Table 3.

Discussion

Consistent with previous reports [10–14], the use of BBs by patients with AHF on admission was high (61.8 %), and it further increased by 24 % during hospitalization. These

findings suggest that to a large extent the use of BBs in AHF has been successfully incorporated into medical practice, particularly in reference cardiology centers, reflecting a correction of the underutilization described in previous years [15]. Our data indicated that 72.7 % (n = 141) of patients were discharged using BBs. These findings suggest that in addition to being incorporated into clinical practice, there is a potential limit for BB tolerability. In our study, this limit appears to be between 70 and 80 % of admissions, which is clearly below the tolerance studies of these drugs in chronic HF, in which tolerability ranges from 92 to 96 % for metoprolol and carvedilol [16–19]. This difference in tolerability is likely to reflect the variation in the disease severity of patients admitted to reference institutions.

The reasons for not using BBs during hospitalization have rarely been addressed, but they may be useful to understanding the possible limitations to the tolerability of these agents in specific subgroups of patients. It is important to consider that BBs are closely related to a negative inotropic and chronotropic effect, lower blood pressure, and increased BNP level, and that these effects are more pronounced at the beginning of therapy, even at low doses, as the benefits of BBs become more evident only after 3 months [5, 6, 20]. While the presence of bronchospasm, bradycardia, and hypotension are objective data constituting absolute contraindications for the initiation of BB therapy, other medical conditions may be more subjective, such as a tendency to hypotension or low clinical output, pulmonary edema that is difficult to treat, asthenia, and fatigue. Such situations may therefore not be explicit in medical records, especially in observational studies. Therefore, the implementation of clinical protocols for AHF that do not clearly explain the conditions under which BB use is controversial or potentially dangerous should be reviewed.

Dharmarajan et al. [21] recently demonstrated that in the United States, more than 40 % of patients with AHF receiving BBs in the acute phase had at least one absolute contraindication. The authors suggested that this practice should be evaluated and that studies on the inappropriate use (overuse) of medications should be considered to avoid the treatment of patients at high risk for severe adverse events.

A marked trend of increasing prescriptions has been noted in recent years, from 37 % in a EuroHeart Failure Survey in 2003 [15] to the most recent studies reporting up to 98 % utilization of BBs, excluding patients with contraindications [22], suggesting that rates of underuse have been overestimated. Nevertheless, little is known regarding the extent to which patients in the real world tolerate appreciable doses of BBs without presenting severe adverse events. Another issue to consider is to what extent the severity of heart disease or existing comorbidities may limit BB use, considering the heterogeneity of heart failure syndrome. This concern is especially relevant when one considers that patients with less severe disease can be maintained for long periods without hospitalization, favoring the progressive selection of patients with more severe disease for hospitalization. Currently, many decisions regarding whether to maintain the use of BBs in AHF are based on a single randomized study of 147 patients who

Table 3 Clinical outcomes of patients admitted for acute heart failure worsening, according to tolerability to beta-blockers

	All (194)	*BB*-tolerant (n = 141)	*BB*-intolerant (n = 53)	*p* value	RR (95 % CI)
Length of hospitalization, median ± IQR	16.9 ± 15.5	**11.0 ± 12 (2–72)**	**18.0 ± 25 (3–82)**	**<.001**[†]	–
Acute renal failure, % (n)	39.2 (76/194)	36.9 (52/141)	45.3 (24/53)	.29	1.23 (0.85–1.77)
Infection, % (n)	7.7 (15/194)	5.7 (8/141)	13.2 (7/53)	.08	2.33 (0.89–6.1)
Sepsis and septic shock, % (n)	15.5 (30/194)	**9.9 (14/141)**	**30.2 (16/53)**	**.001**[*]	**3.02 (1.59–5.75)**
Electronic device implant[a], % (n)	10.8 (21/194)	10.6 (15/141)	11.3 (6/53)	.90	1.06 (0.43–2.58)
Vasoactive amine use, % (n)	23.2 (45/194)	**16.3 (23/141)**	**41.5 (22/53)**	**<.001**[*]	**2.55 (1.56–4.16)**
DVT/PT[b], % (n)	1.5 (3/194)	1.4 (2/141)	1.9 (1/53)	.81	1.33 (0.12–14.37)
ICU[b], % (n)	36.6 (71/194)	32.6 (46/141)	47.2 (25/53)	.06	1.45 (0.99–2.10)
Death during hospitalization, % (n)	8.2 (16/194)	**2.98(4/141)**	**22.6 (12/53)**	**<.001**[*]	**7.93 (2.67–23.49)**

Data are expressed as relative frequency; numbers in parentheses indicate absolute numbers of individuals unless otherwise indicated.

Chi-square test was used to compare qualitative variables. Quantitative continuous variables are expressed as mean ± SD, when demonstrating a parametric distribution, or median ± interquartile range, when demonstrating non-parametric distribution

PT pulmonary thrombosis, *ICU* intensive care unit

[†] Mann–Whitney test, * Pearson Chi square

[a] Electronic device implant includes cardiac resynchronization therapy, implantable cardioverter defibrillator, and pacemaker. [b]DVT, deep venous thrombosis

had previously used these agents for at least 30 days and who were admitted without hypotension, bradycardia, bronchospasm, or hypoxemia [4]. However, this study should be considered insufficient in terms of patient safety.

Patients who did not tolerate BBs during hospitalization in the present study had lower median SBP, lower incidence of hypertension, and increased frequency of chronic kidney disease. In our cohort, they presented a higher frequency of adverse clinical outcomes including frequency of sepsis, use of dobutamine, average length of hospitalization, and death. In one study on the safety and tolerability of BBs in elderly patients during hospitalization for AHF [14], the authors initially excluded 27 % of patients evaluated for the use of BBs among 164 consecutively admitted patients, and 9 % additionally had their treatment interrupted. The authors did not report the hospital mortality rate of those initially excluded, and the reported tolerability only applied to survivors. In another observational study [23], while suggesting that BBs should be used on patients with AHF during hospitalization, the authors pointed out important differences between patients selected and ruled out for the use of these agents. Clinical characteristics clearly differed across patients grouped according to previous use and prescription of BBs on admission, and the hospital mortality rates in the subgroups excluded from BB use on admission were 3–10 times higher than those in the subgroups in which BBs were initiated or maintained. Notably, to date there is no evidence that BBs have any effectiveness in terms of reducing mortality during hospitalization for AHF; therefore, future research should be directed at investigating whether such patients should receive BBs on admission rather than to assign the excess risk of death for not using these agents.

Finally, the OPTIMIZE-HF study [24] has been referred to as evidence that all patients should use these agents, given that those excluded from BB therapy had a poorer prognosis. This argument is inaccurate, however, since OPTIMIZE-HF is an observational study. In the absence of an explicit reason not to use BBs, it is likely that clinical judgment interfered and that these patients had a higher severity of AHF. In general, the under-utilization of a drug is more readily studied and understood than its inappropriate use, which in turn may persist until potential adverse effects can be recognized with sufficient frequency in certain subgroups to draw the attention of researchers. This issue is particularly challenging in the context of BB use in AHF due to the nature of their adverse effects, which overlay the natural course of the disease. In addition, more safety studies involving unstable patients or patients with more severe AHF will be required. At the moment, there is no evidence to insist on the early use of BBs in patients with more severe disease for the sole aim to ensure their future use.

An important consideration in this study is that it was conducted in cardiology reference centers, which are often associated with a higher prevalence of more severe patients. The fact that the study was based on the review of medical records may also limit the availability of some information. However, we believe that our findings have demonstrated external validity in relation to other reference centers that serve a large number of patients with AHF in Brazil and worldwide. In future studies, patients should be evaluated in multiple centers, focusing on services that treat patients with AHF but are not specialized for this patient profile.

Conclusion

Beta-blockers could be used in 72.7 % of patients hospitalized for AHF in this cohort. Patients who could not tolerate BB presented a higher frequency of adverse clinical outcomes including sepsis, hypotension, average length of hospitalization, and death.

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