Levosimendan in Patients with Decompensated Heart Failure

Heart failure is considered a public health problem in several countries and, unlikely other common cardiovascular diseases, its prevalence is on the rise as the elderly population, in whom the prevalence of this pathology is higher, increases.

The pictures of decompensated heart failure (DHF) represent the third cause of hospitalization and the first cardiovascular one in Brazil, presenting high mortality[1]. Thus, the development of therapeutic strategies capable of preventing death by DHF and improving the quality of life of these patients has become a challenge. In this sense, the BELIEF study proposes the use of levosimendan as the inotropic agent of choice for the treatment of DHF.

The study subjects selected for the BELIEF study had important systolic ventricular dysfunction (SVD) and developed decompensated left heart failure (LHF) without hypotension, even after high doses of diuretics.

To our knowledge, these subjects do not represent the majority of the patients with SVD that develop decompensated LHF, as this group of patients usually presents arterial hypotension and, sometimes, renal failure during cardiac decompensations[2].

We want to emphasize that the patients that develop LHF and hypertensive response frequently present normal systolic ventricular function and are treated with vasodilators and diuretics[3]. This group of patients, with normal ejection fraction, represents half of the total number of patients with HF and are not included in the BELIEF[4] study.

Finally, it would be relevant to identify the factors that trigger the cardiac decompensation, such as infections, pulmonary thromboembolism, acute renal failure, arrhythmias, anemia, ischemia, lack of therapeutic adherence, underlying disease progression, alcohol use and sodium overload, as, in many

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"BELIEF": Believe It or Not

cases, the correction of this factor is essential for the institution of adequate management and the observation of a favorable clinical response in decompensated heart failure[5].

The BELIEF[1] study, recently published at *Arquivos Brasileiros de Cardiologia* and carried out at several Brazilian research centers, proposed to assess the efficacy and safety of levosimendan use in patients with decompensated heart failure. We think that the study was not designed to test the efficacy and safety of the medication. The authors were careful when concluded that levosimendan might be a short-term alternative for decompensated heart failure management. However, this interpretation is not supported by the study results and the previously published randomized clinical trials. We present here an opposing view, indispensable for the shaping of clinical knowledge and therapeutic practices[2].

The BELIEF study has a cohort design, and therefore, is an observational, multicentric, non-comparative and open study, on the use of levosimendan in patients with decompensated

heart failure. Hence, it cannot test or verify the efficacy and safety of the drug. It is, in fact, a series of 182 cases. All cases received the intervention and, therefore, it is not possible to conclude about its efficacy, which can only be demonstrated from comparative studies, preferably randomized ones[3]. It is not adequate to evaluate the safety of treatment, either. Common adverse events can only be detected in comparative studies, as it is impossible to isolate adverse events caused by the nocebo effect[4]. Rare adverse events, not detected even at phase-III clinical trials, cannot be isolated either in small series of cases, requiring extensive pharmacovigilance programs (phase IV), previously or after the drug approval for clinical use.

The BELIEF study seems to be a seeding study. Seeding studies aim at familiarizing doctors with a new medication, involving multiple researchers with broad geographic distribution and do not constitute actual scientific contribution, but only a marketing strategy[5]. The severe limitation of the study design, alone, prevents believing on its results. At the study presentation, examples of this limitation can be identified. Patients with a broad spectrum of heart failure (HF) presentation were selected, from patients with the first HF admission to patients that were refractory to inotropics. The inclusion of less severe cases that used levosimendan per protocol prevents the isolation of the drug efficacy. The so-called drug responders (139 of the 182 studied patients) were the less severe cases, which, per se, would tend to be discharged without the use of vasoactive agents.

There is clear evidence of this fact in Table 2, where it is shown that dobutamine was previously employed by 58.1% of the non-responders and only 24.5% among the presumably responders to levosimendan. The other outcomes that characterized the responders, such as lower congestion and dyspnea (Chart 3) were also expected, since these were less sick patients. The primary outcome was, literally, hospital discharge with no need for additional inotropic therapy. The 141 patients that were already off inotropic drugs at the moment of the levosimendan would not reach the study outcome, unless the drug were deleterious.

The best part of discussion of results is the acknowledgement by the author that the study has a fatal shortcoming (literally): "One of the limitations of the present study is the fact that it is an open, non-randomized study. Additionally, the lack of a placebo group prevented the determination of the cause-effect correlations between the treatments and the results". This interpretation recognizes that our main criticism was right and that we finally agree with the authors. If it is impossible to determine a cause-effect relationship between treatment and outcomes, the study is useless. In the following sentence, subverting the logic (reverse scholasticism), the authors affirm (literally) that "the systematically favorable results and the low incidence of adverse events must be attributed to levosimendan use".

In addition to the aforementioned limitations, the BELIEF study needs to be compared to other studies. The SURVIVE[6] study had previously answered the research questions raised by the BELIEF study in a comparable, randomized and double-blind context. In this study, which included 1,237 patients, the 6-month mortality was identical among patients treated with dobutamine and levosimendan. The only significant difference in the results was the higher incidence of atrial fibrillation among those treated with levosimendan. As dobutamine use is associated with increased mortality in patients with severe heart failure, when compared to placebo[7-10], we can conclude that, if there is an effect of levosimendan on survival, it is more likely deleterious.

The last point that needs to be addressed is the absence of disclosure of potential conflict of interest by the study authors. If there are none, this should be explicitly stated, according to the requirements of the journal. This aspect is particularly important, because throughout the study (and not under the necessary highlighting, in the title page), we learn that the BELIEF study is part of a program of early access to levosimendan, presumably sponsored by the pharmaceutical industry. In "Methods", one can also find the declaration that the sponsoring industry collected and processed the study data, which had its statistical analysis carried out by a external consulting group and not at the centers that led the research. It was informed only that the authors checked the results. The conduction of studies by the sponsor does not necessarily means willful misconduct in its planning, analysis and interpretation, but it favors bias, being a questionable practice nowadays and needs to be at least clearly informed to the reader. Not only did the authors fail to declare the potential conflicts of interest, but the author of a laudatory editorial commenting the study[11], Dr. Follath, did not state that he is the recipient of remuneration fees from the Laboratory that manufactures levosimendan, as he did in other publications[12].

Studies with a seeding profile, such as the BELIEF study, are still very common in several areas of pharmacological and non-pharmacological therapies. The absence of the scientific essence in these studies and the fact that they can disseminate the use of less effective or ineffective treatments (putting pressure on the payers), require caution on the interpretation of their results, surely precluding the publication of seeding studies in renowned journals. The decision to use or not to use levosimendan in the management of patients with severe heart failure is very far from the results and the interpretation of the BELIEF study.

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"Among the blind, a one-eyed man is king."

THE AUTHOR REPLY

I thank the authors for the letter to *Arq Bras Cardiol* and for their interest in the BELIEF study. The letter demonstrates that this study has already had an important impact in the scientific environment. Additionally, the issue of positive inotropic use in heart failure always raises debate that must be safeguarded against any commercial interest.

Before detailing the authors' points of view, it is important to review some concepts:

1) When reviewing the elementary principles of research (Wikipedia, the free encyclopedia and the Research Manual for Scientific Initiation of the Heart Failure Unit) we could state that the clinical trials with drugs, after the experimental phase in animals, can be divided in Phases 1, 2, 3 and 4[1]. In brief, in Phase 1, the authors verify the initial safety of the drug in a limited number of patients and investigate its efficiency. Randomization is not necessary. After potentially encouraging initial results, phase 2 is initiated with a larger sample size, aiming at analyzing drug effectiveness and maintaining the safety monitoring through the events in the studied population. The studies are often randomized or controlled at this point. After attaining good results in this phase, multicentric, randomized, double-blind studies with large sample sizes are planned.

Hypotheses are tested, such as: is it better when compared to the usual treatment? If not, is it worse than a therapeutic option? And so forth. Again, the safety is assessed in the studied population. These Phase-3 studies are usually carried out in a selected population that might not reflect the general population. In phase 4, the effects on the general population are monitored based on the approval of its use, based on the Phase 3 studies. It is worth mentioning that, due to the restricted inclusion criteria in Phase 3, it is possible to have new findings in Phase 4.

2) Another concept is that studies carried out with different populations, mainly regarding ethnicity, etiology and age, can have different results[2]. It is important to remember that results of studies carried out with populations from other countries (especially non-Latin American ones) might not be true for Brazil, as we have a higher ethnic diversity (African-Brazilian), higher diversity of population origin and etiology (for instance: Chagas).

In Brazil, we must also take into account different state profiles. When comparing the state of Rio Grande do Sul (in the southern part of the country) with the population of many of the Brazilian states, we observe that practically there is no Chagas disease and that there is a low incidence of Black, Mulatto or Asian individuals. For instance, it can be said that those born in Rio Grande do Sul are more similar to Argentineans from Buenos Aires due to the population profile than to the rest of the Brazilian population. Thus, in Brazil, we cannot reason with only one state, but with the whole country, where there is a great deal of diversity.

3) Another important concept is that, in clinical practice, the doctor has to use the best available information to aid his/her decision, using them sensibly in the wealth of Medicine as an Art, never becoming a "slave" of one or other result. This is a fundamental concept, especially for drugs that been approved for use and have never been tested in a specific population, such as the Brazilian one, with its rich diversity.

4) It is also interesting to review some items that are necessary to establish the concept of "seeding trials"[3,4]. Among these, one can observe (1) the need for recruiting investigators based on the fact that they are frequent prescribers of competitive drugs of the same therapeutic class, instead of the investigators' expertise or the fact that they are leaders in the area, (2) study design that is not compatible with

the objectives, (3) payment that is disproportional to the performed work, (4) support of the marketing division and (5) minimal appraisal of the obtained data, objectively assessed by their non-publication. That is, the intention would be just to train physicians in their use, without showing the scientific community the results of the investigation.

Specifically regarding the points discussed by the authors of the letter, it is not possible to agree with most of them, except those that have been specified in the BELIEF text and are repetitive: As follows:

• Regarding the fact that it is a seeding trial: when reviewing the definition of a seeding trial in articles published in high-impact journals, it is verified that the authors of the letter have made a mistake, as the BELIEF study clearly does not meet these criteria[3,4]. Additionally, the data publication further prevents any possibility of defining it as a seeding trial, as the study results are presented to the scientific community for its appraisal. It is even possible that the initial idea of the BELIEF study originated from the intention of private enterprises to disseminate the use of drug that had already been approved in Europe in a population that could benefit from it[5]. It is widely known that, in all studies and at any phase (1,2,3 and 4) the industry investment has the final objective of implementing the use of its product. It was the responsibility of the GEIC Board of Directors, at the time contrary to any study that bore any resemblance to a seeding trial, the task of shaping any possible intention and transforming it into a Phase 2 or Phase 1 study, planning the publication of its results.

This is demonstrated by the fact that, based on the results of the BELIEF study, the multicentric, randomized RELIEF (Randomized Evaluation of Levosimendan Efficacy) study was planned in Brazil, coming very close to accomplishment, having been approved by many Ethics Committees in Research and failing to proceed close to the phase of patient inclusion due to financial support difficulties.

• Regarding the non-publication of the BELIEF study: To publish it was a correct decision made by the reviewers and the Editor of *Arq Bras Cardiol*. considering that, without the publication of the BELIEF study, we would have been deprived of any scientific information regarding the use of levosimendan in a typical Brazilian population, and this could have been a characteristic of seeding trial.

It is worth mentioning that levosimendan has been approved for clinical use in Brazil and has been indicated by clinical cardiologists and specialists in intensive therapy. These doctors have reported, mainly in Congresses, varied experiences depending on the selection of patients that used it. Not to report the data from the BELIEF study, which can help all Brazilian physicians, would be "scientific selfishness" and would be equivalent to be the one-eyed man among the blind. Additionally, it would be a mistake to underestimate the capacity of Brazilian doctors, by considering that their decision will not take into account all the variables for each case, including options, therapeutic responses, study power with its obvious limitations, etc. It is evident that this is a Phase 2 or Phase 1 to 2 study, and/or transition study. Therefore, any increase in its scope is merely an extrapolation.

At the conclusion of the BELIEF study, the authors recommend that, based on the results, a multicentric study specifically focused on the Brazilian population, should be developed;

• The BELIEF cannot test or prove the efficacy and safety of the method: It is not possible to agree, as in all phases of investigation studies, considering their limitations, the efficacy and safety are tested, whether exploratory or not, and these are never definite until phase 4 is reached. There is a sequence of phases to be developed and Phase 3 cannot be carried out without a previous Phase 2, as in the case of BELIEF;

• Limitation of the study design: Most of the study limitations reported by the authors of the letter had been included in the publication, so that the doctor could use the information in the BELIEF study in clinical practice, whether for clinical use or not, in a balanced way. But the BELIEF study has advantages, as it introduces the use of "real-world" patients, as in the studies, < 10% of the patients can be included, i.e., most trials do not reflect the real world[6];

• The so-called responders were the less severe cases: This statement is redundant, as it is of general knowledge that more severe patients usually respond less well to medications, mainly in decompensated heart failure. It would not have been different in the BELIEF study. However, it is not possible to agree that alone, they would tend to be discharged without the use of vasoactive agents, based on the criterion of inclusion of patients that needed positive inotropics. It is obvious that the criterion for the administration of positive inotropics can be diverse in different Centers, but to think that most Heart Failure Centers, with GEIC members, erroneously indicated the inotropics would be to underestimate the capacity of the Brazilian cardiologist. Thus, if most patients needed inotropics and the latter were not administrated, the majority would not have been discharged from the hospital;

• The statement that the Brazilian authors subverted the logic: this affirmation is too simplistic to be accepted. Once again, we recall the basic principles of the investigation, which must be sequential in this type of study. Not to publish the Phase 2 data to be the one-eyed man among the blind would be unacceptable.

• This phrase is similar to the background criticism that we made about the study: This statement is unclear, but what can be apprehended from it is that the authors of the letter agree with the limitations stated by the authors of the BELIEF study and are being repetitive;

• The BELIEF study must be compared to other studies: Unfortunately, it is not possible to accept that, what is good or bad or neutral, in the comparison with other drugs for Europe and the USA, is necessarily the same for Brazil. It would be an undesirable scientific colonialism, based on the different profile of the studied populations. The BELIEF study presents etiologies, ethnicities and ages that are completely different from the SURVIVE study. Hence, the need for a scientific study that is adequate for the Brazilian population[7]. Again, it is very simplistic, from a clinical point of view, to affirm that dobutamine is related to the increase in mortality in clinical practice, without taking into account other variables in each patient. The association is true when the drug is used inappropriately; however, when used in a "real-life" patient

that is admitted with bad perfusion and congestive picture with systemic blood pressure of 70x50 mmHg, the lack of the use will increase the mortality[8];

• Regarding the conflicts of interest: It is up to the Arq Bras Cardiol to give an answer to that, but the conflicts of interest of the authors of the BELIEF study are clearly stated in the publication. However, in order to improve transparency in this area, the conflicts of interest should not be considered only at the individual level, but extendable to the other involved members of the institution. Often, investigators from different groups at the same institution tend to favor the line of conduct of a partner group, when the latter is supported by external sponsors;

• The sponsor industry collected and processed the data: It is difficult to understand the point of view raised by the authors of the letter sent to *Arq Bras Cardiol,* perhaps because they are not used to multicentric investigations sponsored by the industry. Unfortunately, as I do not favor them myself, the multicentric study data are always collected and analyzed by the sponsor's representatives. The authors of the letter probably have ongoing investigations at their own institution that were carried out in this way. But, contrarily to the suggestion made by the authors of the letter, the study was not planned by the industry.

Therefore, it can be verified that the BELIEF study results must be considered in the light of its scope and its limitations in clinical practice, as it was a consistent study developed by Brazilian investigators, with a large reputation in clinical research. It is a study that stimulates the development of a Phase-3 study in Brazil, specific for the Brazilian population. Philosophically, no one owns the scientific truth, but it is our responsibility to release information to the medical community to improve the decision-making when treating the patient. To be the one-eyed man among the blind is inadvisable; one must strive so that all can see the benefits and limitations of a certain treatment.

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LETTER TO THE READERS

On the subject of the letter: "BELIEF": believe it or not", by Luis Beck-da-Silva and Flavio Danni Fuchs, regarding the study by Bocchi et al[1], the *Arquivos Brasileiros de Cardiologia* acknowledge its failure in publishing the conflicts of interest by the author of the Editorial "Can we Believe in Levosimendan?", Ferenc Follath[2]. That was due to the existence of previously declared conflicts of interest in another recent publication by the same author in the Journal[3]. For record sake, we herein repeat the declaration:

"F. Follath has participated in the Scientific Board of and received remuneration for giving lectures from Abbott Laboratory."

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