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Efficacy of Metoprolol in Reducing Mortality in Patients with Septic Shock. Randomized Controlled Clinical Study

Running Title: *Metoprolol in Septic Shock*

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Abstract: ***Background: Sepsis is one of the most common fatal diseases worldwide; in Mexico it represents 27.3% of intensive care unit admissions, with a mortality of 30.4%. The use of β-blockers, including metoprolol, has been evaluated in different meta-analyses, demonstrating safety; however, it has been concluded that the lack of randomized studies is the limiting factor in identifying its efficacy. Aim Of The Study: To evaluate the efficacy of metoprolol in reducing mortality in patients with sepsis. Methods: Double-blind, randomized, controlled clinical study. Conducted in patients between 18 and 75 years old, admitted to the internal medicine service with a diagnosis of sepsis, managed with antibiotics in the first 6 hours of diagnosis. Eleven subjects were included in the metoprolol-treated group and ten in the placebo group; heart rate, mean arterial pressure, lactate, SOFA index and mortality were evaluated. MAT remained stable in both groups, HR decreased by 16 bpm, while in the placebo group it decreased by only 9 bpm (p=0.050). Lactate values and SOFA index also decreased in the intervention group, only the latter with values of p<0.05. Results And Conclusions:The use of metoprolol decreases heart rate without having a significant effect on mean arterial pressure. As a consequence, it is safe to administer it at the dose considered, and it is plausible that it may have a beneficial impact in reducing mortality in patients presenting with sepsis. The β-blockers are a promising therapy that requires further prospective randomized studies confirming the reported findings.***

Keywords: Metoprolol, Beta-blocker, Sepsis, Mortality, Mortality

1. Background

Sepsis is a global health problem generated by different pathophysiological mechanisms that can lead to patient death (1), including cardiovascular dysfunction that has been shown to increase mortality by 70-80% compared to 20% in patients who do not develop sepsis. Despite the knowledge available regarding the pathophysiology of sepsis and the growing number of antibiotics, mortality remains high, so effective treatments are needed to help improve outcomes in critically ill patients (2). The β-blockers have been used to reduce myocardial oxygen consumption in ischemic heart disease; in the same vein, clinical studies have shown that the use of β-blockers reduces the incidence of complications after cardiac surgery (3). We know that over-activation of the sympathetic nervous system in the context of a generalized bacterial infection is a hallmark of sepsis, which can progress to stress-induced cardiac damage, so β-blockers, whose function is to restrain the sympathetic nervous system, are being studied (4). In sepsis, β2-adrenergic stimulation selectively inhibits Th1 lymphocyte function of CD4+ lymphocytes and favors Th2 responses that inhibit macrophage activation, T-cell proliferation, and proinflammatory cytokine production (5). It is known that metoprolol is a widely prescribed drug that has already been shown to increase survival in patients with other cardiovascular diseases; its accessibility and low cost, as well as its safety in doses of 100 mg per day, can be prescribed at the beginning of the diagnosis of patients with sepsis and septic shock to contribute to the reduction of mortality. The above, through the reduction of lactate levels, as a mediator of the uncontrolled inflammatory response, and by reducing the heart rate (HR). At the same time, the use of high doses of vasopressor drugs is avoided, and cardiac oxygen consumption is improved, increasing the volume at the end of diastole, thus improving cardiac output and tissue perfusion. The aim of our study was to evaluate the efficacy of metoprolol in reducing mortality in patients admitted to the intensive care unit with a diagnosis of sepsis.

2. Methods

To fulfill our objective, a prospective, randomized, double-blind, placebo-controlled, parallel-group clinical study was designed and conducted at the Dr. Valentín Gómez Farías Regional Hospital of the Instituto de Seguridad y Servicios Sociales para los Trabajadores del Estado (ISSSTE) Zapopan Jalisco. Approval was obtained from the ethics committee with registration number **ISSSTE/CEI/432/2020** as well as the signature of informed consent from each of the subjects included in this study. The sample size was calculated with a 95% confidence level (α=0.05), a power of

80% (β=0.2), taking as background the study by Singer et al. (6) where a decrease in mortality of 41% is reported, using the formula for clinical studies (7), which gives us 13 subjects to be included per group. Patient allocation was done by simple randomization with electronically generated random number tables to assign to the experimental and placebo groups. Medicine administration, as well as follow-up and measurement of each study variable, was performed by double blinding.

The study included men and women between 18 and 75 years of age with a diagnosis of sepsis, according to the SEPSIS-3 consensus criteria, admitted to the internal medicine department, in whom antibiotic management was initiated within the first 6 hours of diagnosis. Patients with known neoplastic disease, chronic kidney disease on replacement therapy, cardiogenic shock, first-degree block, sick sinus disease, basal heart rate less than 65 bpm, HCV, HBV, HIV infection, pregnancy, and metoprolol intolerance were excluded. Patients with contraindications for the use of the enteral route were eliminated. Once the patient was admitted in compliance with the selection criteria, we proceeded to administer the drug previously placed in a blister (identical for both groups), the first containing metoprolol 50 mg and the second placebo, administered every 12 days. This dosage was maintained until resolution of sepsis assessed by a SOFA=0 or its baseline SOFA, in addition to negative biochemical markers (CRP and calcitonin). In case the patient had tolerance to the oral route, the ground tablet was administered by nasogastric or gastrostomy tube. For clinical evaluation, heart rate and blood pressure (MABP) were recorded at T0 (baseline), T1 (4 hrs), T2 (8 hrs), T3 (12 hrs), T4 (24hrs), T5 (36 hrs), T6 (48hrs), T7 (60 hrs), T8 (72 hrs) and T9 (96 hrs) after medication was prescribed. Patients with sepsis who progressed to septic shock requiring vasopressor following metoprolol use and vasopressor doses at 24, 48, 72 and 96 hrs in patients with septic shock were identified.

3. Results

Of 52 subjects admitted with a diagnosis of sepsis, only 21 met the selection criteria (**Figure No.1**). The groups consisted of 11 individuals in the metoprolol group and 10 individuals in the placebo group. The average age was 57 years in the intervention group and 58 years in the placebo group, with no statistical differences between the two groups. Most of the subjects analyzed were male. As for the infectious focus, within the metoprolol group, pulmonary (45.5%) was found in first place, followed by urinary (27.3%), and in the placebo group, urinary (50%) was first, followed by pulmonary (40%) (*p=0.330*). Similarly, most patients (90.9% and 90%, respectively) reported no previous use of β-blockers (**Table 1**). The most frequent pathological history was arterial hypertension (54.5% intervention group and 20% placebo group), followed by heart failure (27.3% and 10% respectively), less frequent were a history of ischemic heart disease, tachyarrhythmia, chronic kidney disease and active SARS-COV2 infection (**Table No.2**). After drug administration, two important clinical indicators were monitored: blood pressure and heart rate. Regarding mean arterial pressure, the baseline in the intervention group was 89±18mmHg, while in the placebo group it was 79±13mmHg, with no statistically significant differences between them (p=0.180), the pressure remained above 60 mmHg in both groups for a follow-up period of 96 hours (from T0 to T9), with a final MABP of 82.7 mmHg in the metoprolol group and 81 mmHg in the placebo group, with no statistical differences between groups (**Figure No.2**). Regarding heart rate, baseline measurements were 99.9 ± 13 bpm for the metoprolol group and 93± 11 for the placebo group (*p=0.251*). As for the final heart rate (at 96 hours) it decreased to 83 ±13 in the metoprolol group and from 84 ± 13 in the placebo group (*p=0.750*). In the metoprolol group HR decreased from 99 to 83 bpm, i.e. ΔHR= 16 bpm, on the other hand, in the placebo group HR decreased from 93 to 84 bpm, i.e. ΔHR=9 bpm (*p=0.05*) (**Table No.3**). The initial and final SOFA values of the two groups, as well as serum lactate, were analyzed, a statistically significant difference was observed in the decrease in SOFA in the metoprolol group (*p=0.043*). However, in the placebo group there was no uniform decrease in SOFA, but rather the values were indistinctly distributed from 0 to 14 (*p=0.836*) (**Figure No.4**). Lactate values did not show statistically significant differences between groups (**Figure 5**). Finally, the frequency of mortality in each group was quantified, with a higher percentage in the placebo group (30%) versus 9.1% in the metoprolol group (without statistical differences between groups); a binary logistic regression analysis was performed, calculating a RR of 0.3, which represents protective qualities for metoprolol (95%CI 0.03 - 2.4). On the other hand, analyzing the absence of metoprolol administration as a risk factor in the contingency table, we observed that the placebo group had 3.3 times the risk of death compared to the group treated with metoprolol (95%CI 0.41 - 26.8) (**Table 4**).

4. Discussion and Conclusions

In sepsis and septic shock there is an increase in sympathetic tone in an attempt to optimize cardiac output and maintain tissue perfusion; but this response can be exaggerated and worsened by treatment with exogenous catecholamines, such as noradrenaline, which is the treatment of choice in patients with septic shock (8). Recently, attention has returned to β-blockers as an adjuvant treatment for patient management in different scenarios. Two important clinical effects were found in this study: the maintenance of mean arterial pressure, which we observed remained well above 60 mmHg in both study groups. Likewise, there was a decrease in cardiac output, with an ΔHR of 16 bpm in the metoprolol group superior to the decrease in the placebo group, where the ΔHR had a value of 9 bpm (p=0.050). Morelli et al., analyzed in a clinical study the effects of esmolol on the control of the patient with septic shock, based on the premise that (as with metoprolol) β-adrenergic blockade, may allow heart rate control and limit adverse events related to sympathetic over stimulation (9) In animal models with sepsis, β-blockade appears beneficial, particularly when administered as pretreatment (10) (11). Although heart rate control is likely to improve cardiovascular performance, consideration should be given to the possibility that beta-blocker therapy in human septic shock may lead to cardiovascular decompensation. In this regard, Morelli's study reported a good safety profile in patients in septic shock who were administered oral metoprolol to achieve

heart rates below 95/min. Similarly, in our study, metoprolol administration decreased heart rate in a controlled manner to an average of 83 ±13 bpm. A meta-analysis by Abdullah et al. compiled data from 18 studies, including data from 74 643 individuals with AMI treated early with metoprolol, concluded that compared with placebo, patients receiving metoprolol did not result in a statistically significant reduction in 6-week mortality (OR 0.9 - 1.01). 9 - 1.01); however, a subgroup analysis excluding high-risk patients with Killip class III and higher showed that beta-blockers resulted in a significant reduction in short-term mortality (OR 0.93 CI 0.88-0.99) (12). In the clinical study by Morelli et al., on the other hand, it demonstrated lower mortality at 28 days in patients with sepsis where β-blocker was included early compared to placebo (49% vs 62%, p=0.001) (9). We obtained a RR of mortality in patients who did not receive metoprolol of 3.3 times more compared to the group that received it, however, we obtained a CI of 0.41 - 26.8, so, without being able to be conclusive, we can infer a tendency to statistical significance.

Despite the high worldwide incidence of sepsis, in this study we only managed to meet 80% of the initially estimated sample. Despite having detected 52 subjects with a diagnosis of sepsis, only 21 patients met the selection criteria. As a result, this study can be considered as the interim presentation of the clinical study designed, especially due to the results observed with a tendency to statistical significance, where it is inferred that we are facing a type II statistical error, where increasing the sample size can be reflected in the demonstration of the statistical difference. Among the above reasons is mainly the pandemic, due to the SARS-COV2 virus that forced many institutions, including ours, to make a complete hospital transformation to attend only patients with COVID-19.

One of the most important indicators identified to evaluate the evolution of sepsis is the SOFA index, with a statistically significant decrease (p= 0.048) in the group treated with metoprolol, which can be interpreted as a lower organic deterioration of the patients at the time of discharge. Nevertheless, alternative explanations should be considered, for example, that patients who die generally tend to score higher on the SOFA scale (13). Finally, we note that no patient developed cardiogenic shock, sinus block or bradycardia, which indicates that the dose of metoprolol administered is well tolerated in this population. This should encourage the development of randomized clinical studies that include metoprolol as an alternative to new generation beta-blockers, whose cost and availability is limited in our setting.

Overall, the results obtained in this study indicate that the use of metoprolol decreases the mean heart rate at 96 hours after admission, without having a significant effect on mean arterial blood pressure. As a consequence, it is safe to administer at the dose considered, and it is plausible that it may have a beneficial impact on mortality and increase 28-day survival in patients presenting with sepsis and septic shock; however, further randomized clinical studies with sufficient statistical power are needed to confirm these findings.

References

[1] Weiss S, Peters M, Alhazzani W, Agus M, FLori H, Inwald D, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatr Crit Care. 2020 Feb; 21(2): p. e52-e106.
[2] Espinoza-Villafuerte M, Martínez-Zubieta R, Zaragoza-Galván J. Relación entre consumo crónico de betabloqueadores y mortalidad en sepsis y choque séptico. Med Crit. 2017; 31(2): p. 74-77.
[3] Poldermans D, Boersma E, Bax J, Thomson I, van de Ven L, Blankenteijn J. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. N Engl J Med. 1999; 341(24): p. 1789-1794.
[4] Macchia A, Romero M, Comignani M, Mariani J, Ettorre A, et al. Previous prescription of b blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis. Critical Care Medicine. 2012; 40.
[5] Montmollin E, Aboab J, Mansart A. Bench-tobedside review: β-adrenergic modulation in sepsis. Critic Care. 2009; 13(5): p. 230.
[6] Singer K, Collins C, Flahive J, Wyman A, Ayturk M, Heena P. Outpatien beta-blockers and survival from sepsis: Result from a national Cohort of Medicare beneficiaries. American Journal of Surgery. 2017 Oct; 14(4): p. 577-582.
[7] Velazco V. Muestreo y tamaño de Muestra IMSS , editor. Cd México: e-libro.net; 2003.
[8] Sanfilippo F, Santoncito C, Morelli A, Foex P. Beta-blocker use in severe sepsis and septic shock: a systematic review. Curr Med Res Opin. 2015; 31(10): p. 1817-1825.
[9] Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA. 2013 Oct; 310(16): p. 1683-91.
[10] Mori K, Morisaki H, Yajima S. Beta-1 blocker improves survival of septic rats through preservation of gut barrier function. Intensive Care Med. 2011; 37(11): p. 1849-1856.
[11] Macchia A, Romero M, Comignani P, Mariani J, D'Ettorre A. Previous prescription of β-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis. Critical Care Medicine. 2012; 40(10): p. 2768-72.
[12] Al-Reesi A, Al-Zadjali N, Perry J, Fergusson D, Al-Shamsi M, Al-Thagafi M, et al. Do beta-blockers reduce short-term mortality following acute myocardial infarction? A systematic review and meta-analysis. CJEM. 2008; 10(3): p. 215-223.
[13] Pölkki A, Pekkarinen P, Takala J, Selander T, Reinikainen M. Association of Sequential Organ Failure Assessment (SOFA) components with mortality. Acta Anaesthesiol Scand. 2022 Jul; 66(6): p. 731-741.

Tables and Figures

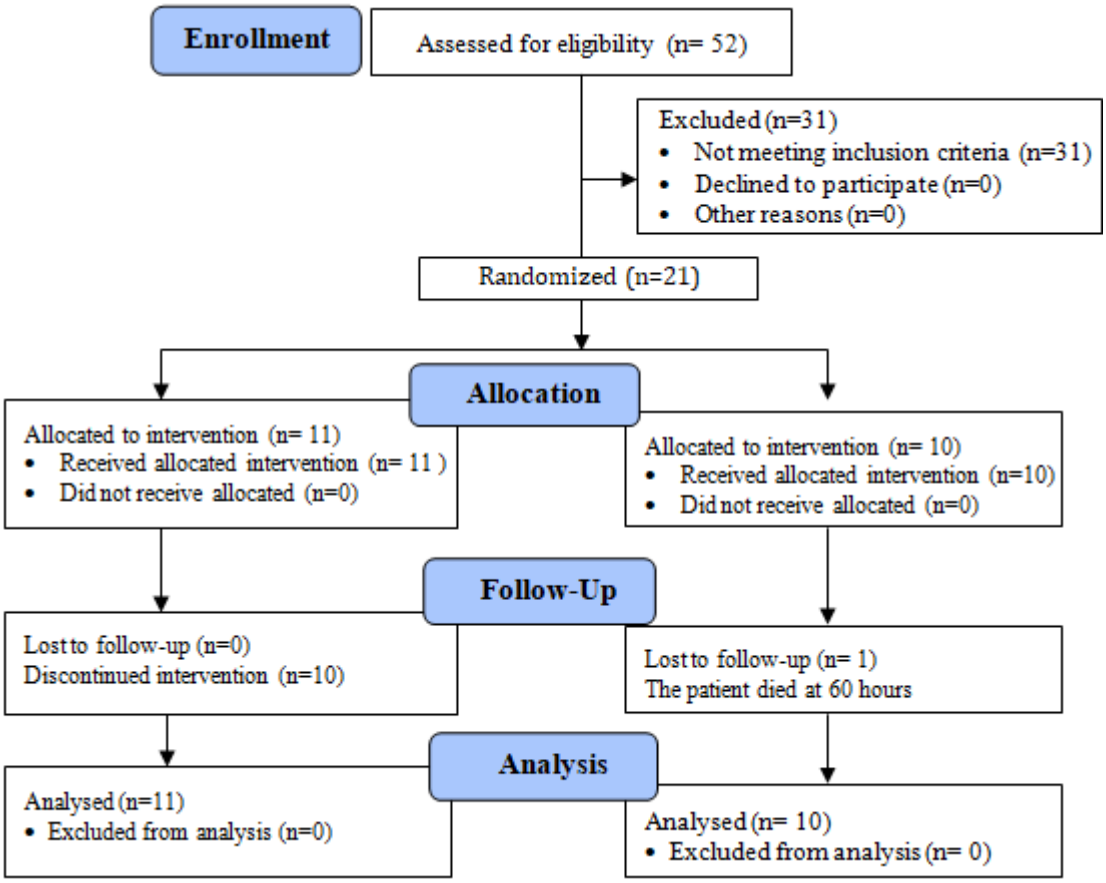


Figure 1: Consort Flow Diagram

Table 1: General characteristics of the study population. Comparison between groups, N= 21

	Metoprolol	**Placebo**	***p***
	n=11	**n=10**	
Age*	57 ± 11	58 ± 12	*0.71*
Sex**			
Feminine	54.50%	60.00%	*0.8*
Masculine	45.50%	40.00%	
Infectious focus **			
Urinary	27.30%	50.00%	*0.33*
Pulmonary	45.50%	40.00%	
Soft Tissues	18.20%	0.00%	
IPGIE	0.00%	10.00%	
Cholangitis	9.10%	0.00%	
Prior use of β-blockers **			
No previous use	90.90%	90.00%	*0.94*
With previous use	9.10%	10.00%	

* The difference between means was determined with the Mann Whitney U test ** The difference between percentages was calculated with the Chi-square test. IPGIE= Infectious Gastroenteriris

Table 2: Personal pathological history. Differences between groups, N= 21

	Metoprolol	Placebo	
	n=11	n=10	*p*
Ischemic heart disease			
No known history	90.90%	90.00%	
Known history	9.10%	10.00%	*0.94*
Chronic Heart Failure			
No known history	72.70%	90.00%	
Known history	27.30%	10.00%	*0.31*
Tachyarrhythmia			

No known history	81.80%	100.00%	
Known history	18.20%	0.00%	*0.16*
Arterial Hypertension			
No known history	45.50%	80.00%	
Known history	54.50%	20.00%	*0.1*
Chronic Kidney Disease			
No known history	90.90%	90.00%	
Known history	9.10%	10.00%	*0.94*
Active SARS-COV2 Infection			
No known history	90.90%	90.00%	
Known history	9.10%	10.00%	*0.94*

* The difference between means was determined with the Mann Whitney U-test ** The difference between percentages was calculated with the Chi-square test.

Table 3 Evaluation of the variation in MABP and HR. Difference between groups, N= 21

	METOPROLOL, n=11	PLACEBO, n=10	*p*
Δ MEAN BREAKING BLOOD PRESSURE (mmHg)	6.3 ± .2	1 ± 0.5	*0.336*
Δ HEART RATE (bpm)	16 ± 3	9 ± 2.5	*0.050*

The difference between means was calculated using Student's t-test.

FIGURE No.2 Variation of MABP during follow-up of the two study groups.

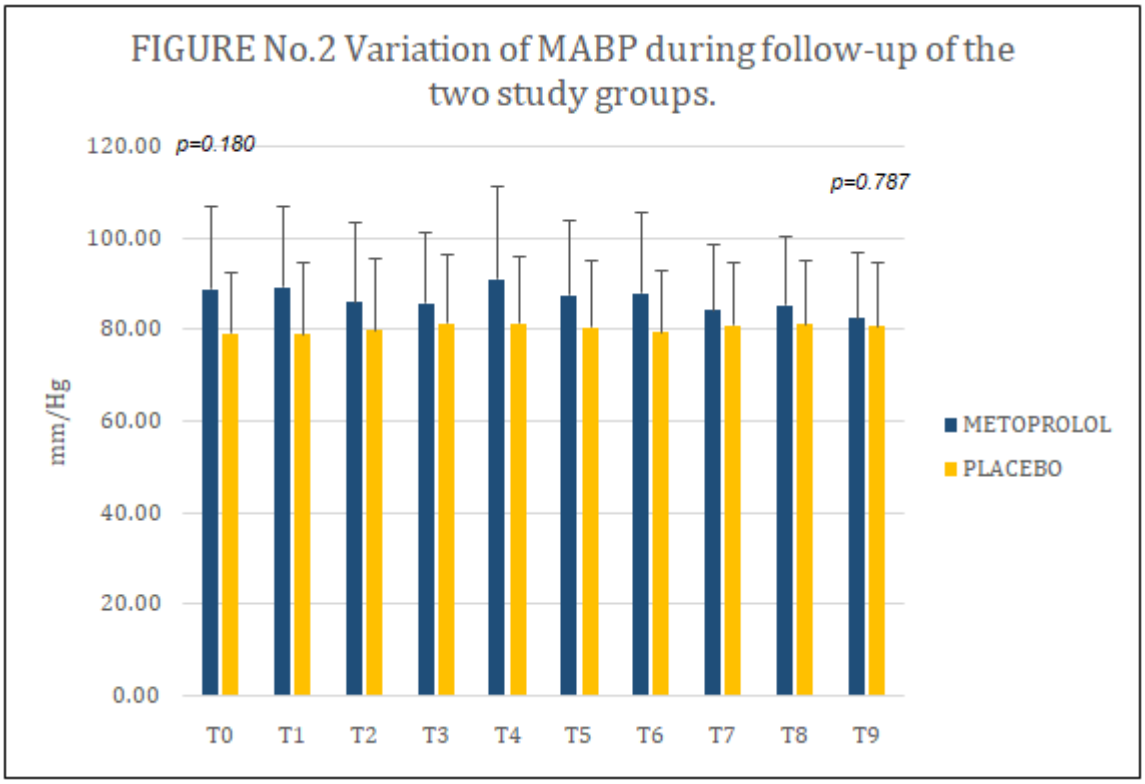


FIGURE No.3 Heart rate variation during follow-up of the two study groups.

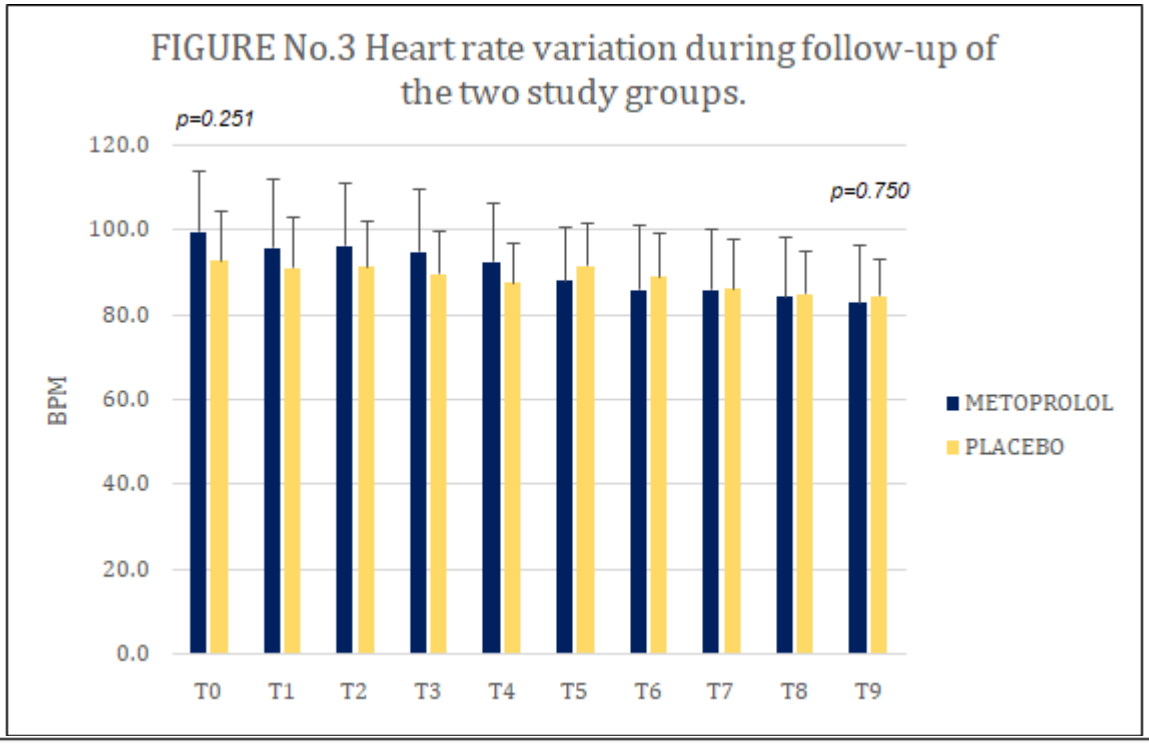
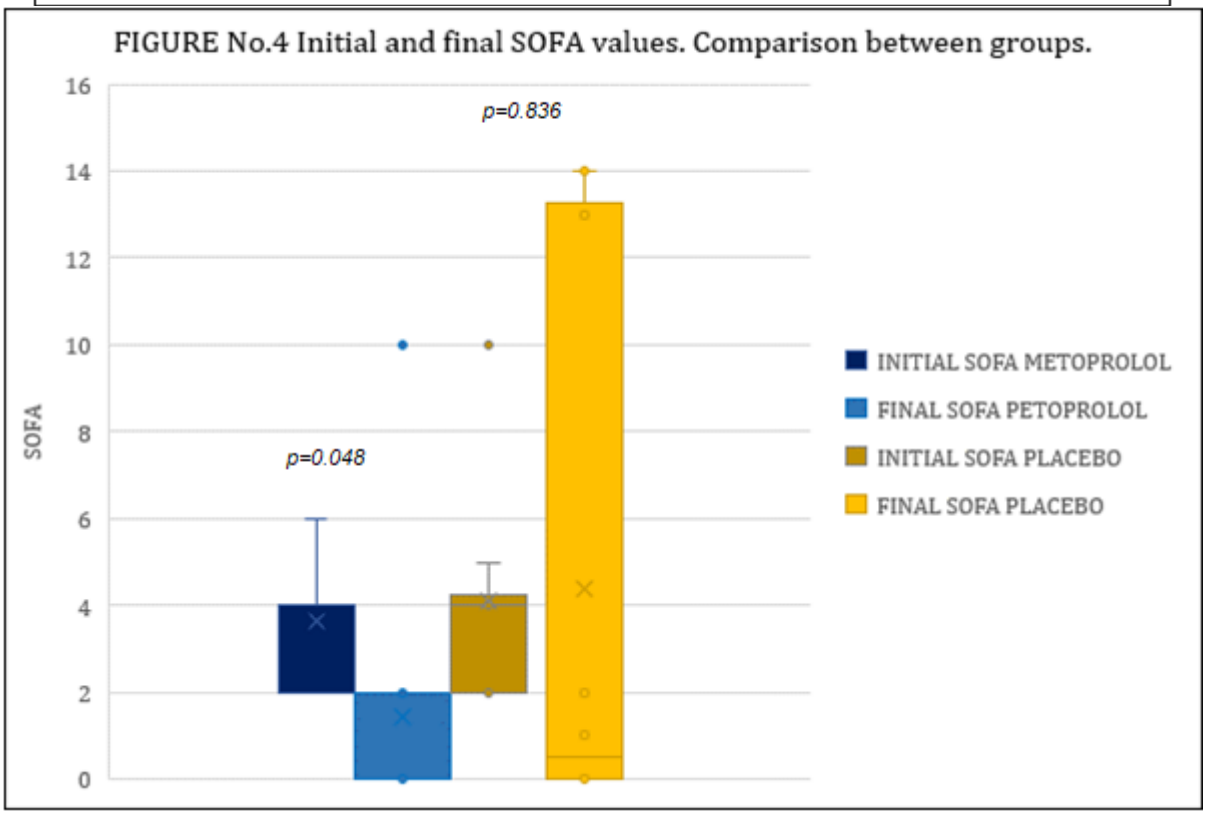


FIGURE No.4 Initial and final SOFA values. Comparison between groups.



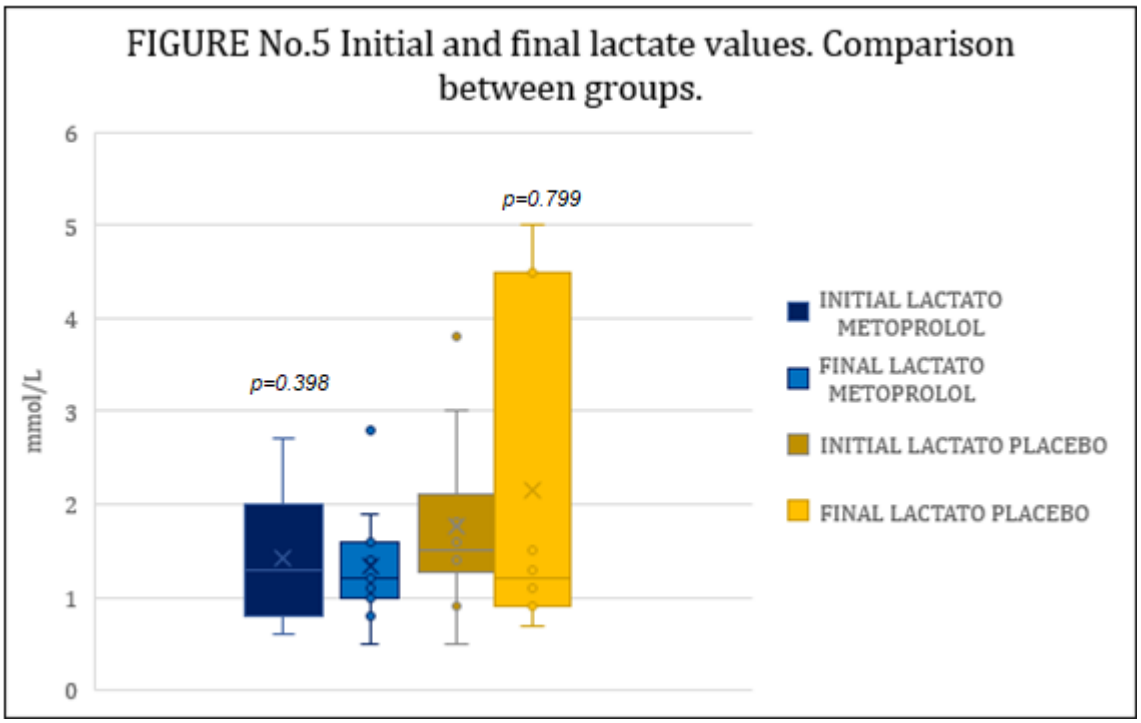


Table 4: Evaluation of mortality in patients diagnosed with sepsis. Difference between groups, N= 21

	METOPROLOL, n=11	PLACEBO, n=10	*p*	RR	IC 95%
DEFUNCTIONS	9.1%	30.0%	*0.223*	0.3	0.03 - 2.4
SURVIVAL	90.9%	70.0%		3.3	0.41 - 26.8