A Randomized clinical Trial of Inhaled Ciclesonide for Acute Asthma.

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Research article

Keywords: asthma, treatment, clinical trial, emergency room

Posted Date: October 7th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-51293/v1>

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Abstract

Background: Current guidelines for management of acute asthma exacerbations advocate the administration of short-acting bronchodilators and systemic corticosteroids. The use of inhaled corticosteroids for this purpose has been tested since the 1990s, but the optimal agent, dose, and strategy have yet to be defined. Within the context, we designed a double-blind, randomized clinical trial aiming to compare high doses of inhaled ciclesonide to systemic corticosteroids in the treatment of acute asthma exacerbations in the emergency department.

Methods: This double-blind, randomized clinical trial enrolled 58 patients with a clinical diagnosis of bronchial moderate and severe asthma by GINA(Global Initiative for Asthma) criteria who presented to the emergency department with peak flow <50% of predicted. Patients were randomized into two groups. Over the course of 4 hours, one group received 1440 mcg inhaled ciclesonide plus hydrocortisone-identical placebo (ciclesonide + placebo group), while the other received 500 mg intravenous hydrocortisone plus ciclesonide-identical placebo (hydrocortisone + placebo group). Both groups received short-acting bronchodilators (fenoterol hydrobromide and ipratropium bromide) as recommended by GINA. The research protocol included spirometry, rigorous and frequent clinical evaluation (dyspnea, accessory muscle use, wheezing, respiratory effort), and vital signs and ECG monitoring. Data were obtained at baseline, 30, 60, 90, 120, 180, and 240 minutes. We compared data from baseline to hour 4 between and within groups.

Results: Overall, 31 patients received ciclesonide + placebo and 27 received hydrocortisone + placebo. Inhaled ciclesonide was as effective as intravenous hydrocortisone in improving clinical parameters (Borg-scored dyspnea, $p=0.95$; sternocleidomastoid muscle use, $p=0.55$; wheezing, $p=0.55$; respiratory effort, $p=0.95$) and spirometric parameters (forced vital capacity, $p=0.50$; forced expiratory volume in the first second, $p=0.83$; peak expiratory flow, $p=0.51$).

Conclusions: Inhaled ciclesonide was non-inferior to systemic hydrocortisone for management of acute asthma exacerbations, improving both clinical and spirometric parameters.

Trial registration: RBR-6XWC26 - Registro Brasileiro de Ensaios

Clínicos (<http://www.ensaiosclinicos.gov.br/rg/RBR-6xwc26/>). Date of registration: 05/01/2016 'retrospectively registered'.

Background

Asthma is a chronic inflammatory disease of the airways that affects approximately 300 million people worldwide. In the United States, between 2001 and 2003, asthma exacerbations caused 4,210 deaths, 504,000 hospitalizations, and 1.8 million emergency room visits¹.

Since the mid-1990s, inhaled corticosteroids have been tested for the management of asthma exacerbations in the emergency-room setting, due to their systemic corticosteroid-sparing potential and

because they avoid the need for venipuncture, which is sometimes difficult^{2,3,4}. These drugs exert vasoconstrictor effects on the mucosa by reducing neuronal reuptake of noradrenaline at the neuromuscular junctions of mucosal vessels, thus reducing secretions and facilitating the delivery of beta-2 agonists to their target receptors; onset of action is rapid, with peak vasoconstriction occurring in 30 minutes and lasting up to 90 minutes after inhalation^{5,6}.

Ciclesonide is a prodrug which is activated at the site of action (bronchial cells and lining fluid of bronchus) by bronchial esterases, converting ciclesonide to desisobutyl ciclesonide, which has 100-fold greater affinity for the glucocorticoid receptor than ciclesonide itself⁷. Because of this peculiar property, common side effects such as hoarseness, dysphonia, oral candidiasis, and suppression of the hypothalamic-pituitary-adrenal axis are much less frequent with ciclesonide than with other high-dose inhaled corticosteroids, as it is inactive outside the lung^{7,8,9,10,11}.

The anti-inflammatory action of intravenous corticosteroids occurs via a genomic mechanism, reducing expression of proinflammatory mediators such as interleukins¹² and upregulating expression of beta-adrenoceptors in bronchial smooth muscle. This effect is also shared by inhaled corticosteroids and begins 4 to 6 hours after administration¹³, although some studies have shown that systemic corticosteroids administered up to 1 hour after emergency department admission in severely ill patients yields clinical benefits, such as reduced hospitalization rate and shorter length of emergency department stay^{14,15}.

Data from double-blind randomized controlled trials suggest that, compared to systemic corticosteroids, inhaled corticosteroids can decrease admission rates and allow earlier discharge from the emergency department. Peak flow levels and FEV1 also rise more quickly in patients given inhaled corticosteroids^{16,17,18,19}.

To the best of our knowledge, this is the first double-blind randomized clinical trial to compare high-dose inhaled ciclesonide versus injectable hydrocortisone for acute asthma management in the emergency setting. This trial is justified by the expected potential for fewer side with inhaled ciclesonide, supposed benefit of its rapid onset of action, and need for more inhaled drugs available for clinicians dealing with asthma exacerbation in the emergency department.

Methods

Population and setting. We studied patients with asthma aged 13 years or older, of both sexes, in the city of São Paulo, Brazil. Patients were recruited from the emergency department of Hospital São Paulo (a teaching hospital of the Federal University of São Paulo) and from two public freestanding urgent care centers affiliated with the hospital: AMA Santa Cruz and AMA Sacomã.

We included patients with a previous diagnosis of asthma (dyspnea, cough, wheezing, chest tightness, associated with allergen exposure or cold air)^{20,21} who received follow-up at outpatient clinics within the

catchment area of the Hospital São Paulo emergency department and had a peak flow <50% of predicted. All participants had a longstanding history of asthma, with repeated exacerbations and emergency room visits. Our included patients had at least 2 years of moderate or severe asthma, with a mean peak flow immediately before intervention of 163 L/min.

We excluded patients with body temperature $\geq 37.8^{\circ}\text{C}$, smokers, pregnant women, patients undergoing psychiatric treatment, patients with a history of heart, liver, kidney, or other disease that might contraindicate corticosteroid therapy, patients who had undergone lung resection, patients undergoing treatment for tuberculosis or mycotic infections of the lung, and patients with tracheotomy or mechanical obstruction of the trachea. We also excluded patients with myopathies or neurological conditions (such as sequelae of stroke or encephalopathies), as well as patients with BMI $>40\text{ kg/m}^2$.

Ethical Aspects. This study was approved by the Research Ethics Committee of the Federal University of São Paulo (judgment number 364240). All patients provided written informed consent for participation in accordance with international regulations for human subject research. When patients were underage, consent was obtained from their parents or legal guardians.

This study is registered in the Brazilian Registry of Clinical Trials (<http://www.ensaiosclinicos.gov.br/>) under accession number RBR-6XWC26.

Sample. We studied 31 patients in the ciclesonide group and 27 patients in the hydrocortisone group. We calculated sample size according to Greenberg²², considering a FEV1 improvement of $0.37 \pm 0.85\text{ L}$ after intervention, resulting in 65 patients for each group.

Study design. This is a double-blind, placebo-controlled, randomized clinical trial designed to compare the efficacy of inhaled ciclesonide versus intravenous hydrocortisone in the management of moderate or severe acute asthma in an emergency department setting.

Blinding. Both blinding and randomization were done centrally at Neuro-Sono Sleep Center, São Paulo, Brazil. Blinding of active ingredients and their respective placebos was achieved by random allocation of four letters – A, B, C, and D – to each of the following products: hydrocortisone, ciclesonide, hydrocortisone-identical placebo, and ciclesonide-identical placebo. After random allocation of letters to designate each product, we defined two product pairs, Inhaled Active Ingredient + Intravenous Placebo and Intravenous Active Ingredient + Inhaled Placebo, in a random combination that enhanced the safety of blinding. Both the intravenous placebo and the inhaled placebo were identical to their active counterparts.

Information about the intervention that each patient randomized to the study would receive was distributed in opaque, numbered envelopes, which were only opened at the time of use. The nursing staff prepared the medications for administration as instructed in the numbered envelopes. The staff who prepared the medications, the providers who administered them, and all researchers involved were blinded to the active pharmaceutical ingredients of interest.

Randomization. Patients included in the sample were recorded consecutively in a logbook and assigned a serial number.

The 58 patients were divided into 2 groups: study (Ciclesonide) and control (Hydrocortisone), according to two computer-generated random number tables. Each table contained an ascending sequence of numbers. Patients were allocated to one or the other according to the serial number attributed at the time of enrollment, which ensured that neither staff nor patients were aware of the intervention to which each patient would be allocated.

Ciclesonide Group. Patients received ciclesonide at a dose of 160 mcg/puff. The first dose was administered 5 minutes after inclusion in the trial, and consisted of 3 puffs (480 mcg); the second dose at 20 minutes (480 mcg); and the third dose at 40 minutes (480 mcg), for a total of 1440 mcg. Patients in this group also received hydrocortisone-identical placebo at 5 minutes.

Hydrocortisone Group. Patients in this group received 500mg of hydrocortisone intravenously and ciclesonide-identical placebo at 5, 20, and 40 minutes.

Both Groups. Both groups received short-acting bronchodilators (fenoterol hydrobromide and ipratropium bromide) at 0, 10, and 30 minutes.

Measures. We adopted as a primary outcome measure the spirometric variables FEV1 and peak expiratory flow (PEF), as well as the clinical variables dyspnea, wheezing, and accessory muscle use during breathing (assessed by observation of the sternocleidomastoid muscle). As secondary outcomes, we evaluated the heart rate, respiratory rate, blood pressure, and pulse oximetry.

These parameters were measured every 30 minutes from the time of patient admission until the second hour and every 60 minutes thereafter until the fourth hour in the emergency department, for a total of 7 measurements, ensuring rigorous monitoring throughout the patient observation period. For the purposes of this study, we analyzed data from baseline and the fourth hour, as we felt these assessments were sufficient to represent the patients' course among the 7 measurements obtained.

Procedures. The emergency room nurse applied the Manchester Triage System and measured oxygen saturation, blood pressure, and breathing pattern. The emergency room physician then confirmed the diagnosis of asthma exacerbation and notified the investigators, who performed an initial assessment by measuring peak flow and explaining the study to the patient. Patients with a peak flow less than 50% of predicted were invited to participate in the study (Figure 1), as the sample was designed to include only severe patients.

Once the patient was included, the investigators worked with the emergency department staff to provide all necessary care and perform the measurements required for the study.

Spirometric parameters were measured in an Easy One model 2009 spirometer (nidd Medizintechnik AG, Zurich, Switzerland). The best of three successive expiratory curves was considered valid and used for

analysis, as recommended by the American Thoracic Society. Peak flow was estimated with the Mini-Wright Peak Flow meter (Clement Clarke, Hanlon, United Kingdom). Again, the highest of three measurements was considered for analysis. Dyspnea was assessed subjectively as perceived shortness of breath, using the Borg scale, a visual analogue scale of 0 to 10 where 0 is absence of dyspnea and 10 is maximal dyspnea. During the initial assessment and at each time point of reassessment, we evaluated wheezing and accessory muscle use. Wheezing was assessed through pulmonary auscultation and ranked from 0 to 3 on an ascending scale of severity (0: no wheezing; 1: slight wheezing; 2: moderate wheezing; 3: severe wheezing). Accessory muscle use was also measured on a scale of increasing intensity (0: no accessory muscle activity; 1: slight activity; 2: moderate activity; 3: marked accessory muscle activity). When there was little wheezing or a silent chest plus marked accessory muscle use or signs of muscle fatigue, dyspnea was classified as severe. Individual and pooled analyses were performed for all parameters.

Criteria for Improvement. Patients were evaluated for improvement at all time points of assessment, to ensure patient safety and detect possible need for additional interventions other than those provided for in the study protocol. For the purposes of this study, we considered the following definitions of improvement: 1) FEV1 and PEF $\geq 70\%$ predicted for age, sex, weight, and height; 2) Improvement of dyspnea: a) Borg score $< 2^{23}$; b) reduction of wheezing severity from baseline; and c) no accessory muscle use, as determined by observation of the sternocleidomastoid muscles.

Interim Analysis. We planned an interim analysis for when the number of patients included had reached approximately half the predicted sample size, to decide whether to continue or terminate inclusion. This analysis was carried out at the randomization and blinding center (Neuro-Sono Sleep Center) by a committee established specifically for this purpose. After inclusion of 58 patients, the Interim Analysis Committee suggested that the study be interrupted, since no difference between treatments was detected.

Adverse Events. We actively evaluated the more frequent adverse events, such as dry mouth, tremor, palpitations, anxiety, headache, and recorded any other patient-reported events^{24,25}. These variables were evaluated by intention to treat (ITT).

Statistical Analysis. The sample size was calculated considering a change in FEV1 of 0.37 L, after treatment, as an indicator of improvement; a standard deviation of 0.85 L; a significance level of 5%; and a statistical power of 80%^{16,22}, resulting in a sample size of n=130 patients, i.e., 65 patients in each group. As noted above, interim analyses were carried out as planned after enrollment of 30 patients in each group; at this time, in view of the results, the interim analysis committee recommended termination of enrollment.

Quantitative variables were expressed as mean $\pm$ SD, and categorical variables, as n (%). We used Student's *t*-test for independent samples for normally distributed data, the Mann–Whitney U test for asymmetrically distributed data, and Pearson's chi-square test or Fisher's exact test for categorical data^{26,27}. Outcomes were assessed by ITT, considering the worst scenario, i.e., losses in the study group

were considered treatment failures and losses in the control group as successful treatment. P-values < 0.05 were considered statistically significant.

Availability of Data and Materials. All data generated and analysed during this study are included in this published article (supplementary information files).

Results

Thirty-one patients in the ciclesonide group and 27 patients in the hydrocortisone group were analyzed by ITT.

Demographic Data. The ciclesonide and hydrocortisone groups (Table 1) were similar in age, systolic blood pressure (SBP), diastolic blood pressure (DBP), and proportion of smoking, hypertension (HTN), diabetes (DM), and alcohol use. There were more women in the ciclesonide group ($p < 0.001$).

Table 1
Clinical and demographic characteristics of the ciclesonide and hydrocortisone groups.

GROUP			
Variable	Ciclesonide (n = 31)	Hydrocortisone (n = 27)	p-value
Sex: female, n (%)	23 (74)	18 (66)	< 0.001
Age (years)	38.3 ± 13.58	39.0 ± 18.99	0.826
BMI (kg/m ²)	25.9 ± 5.75	28.0 ± 5.44	0.094
BMI (Minimum e maximum)	(17.51–38.20)	(18.47–39.26)	
SBP (mmHg)	120 ± 14.27	127 ± 14.55	0.057
DBP (mmHg)	78 ± 12.34	75 ± 17.85	0.477
Former Smokers	9 (29.0)	8 (30)	0.960
HTN, n (%)	3 (10)	6 (22.0)	0.175
DM, n (%)	0 (0.0)	0 (0.0)	0.180
Alcoholism, n (%)	1 (3.2)	1 (3.4)	0.920
Obesity, n (%)	7 (22.58)	10 (37.03)	0.727
BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure. HTN, hypertension. DM, diabetes mellitus.			

The ciclesonide and hydrocortisone groups did not differ regarding vital signs and pulse oximetry (Table 2). On within-group assessment, as expected, HR and RR were lower at hour 4, which is consistent with the clinical improvement observed in both groups. On between-group analysis, pulse oximetry and vital signs were not different at hour 4.

Table 2

Response to treatment with hydrocortisone and ciclesonide, at hour 4, considering heart rate (HR), respiratory rate (RR), O₂ saturation (SpO₂), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

Variable	Ciclesonide (n = 31) (m ± SD)	Hydrocortisone (n = 27) (m ± SD)	p	Absolute effect size (95% CI)
HR	86 ± 23.14	90 ± 11.30	0.404	4.0 (-13.19, 5.19)
RR	18 ± 3.74	18 ± 5.52	0.679	0.0 (-2.46, 2.46)
SpO ₂	97 ± 3.19	95 ± 3.40	0.144	2.0 (0.30, 3.70)
SBP	120 ± 15.64	127 ± 14.32	0.092	7.0 (-14.71, 0.71)
DBP	75 ± 9.07	79 ± 12.31	0.208	4.0(-9.64, 1.64)
m = mean; SD = standard deviation; CI = confidence interval				

Clinical Variables. All clinical parameters evaluated in this study showed improvement at hour 4 as compared with hour 1 (baseline). There was also no difference between the effects of ciclesonide and those of hydrocortisone at hour 4, i.e., both treatments were equally effective in improving respiratory effort, accessory muscle use, wheezing, and Borg Dyspnea Scale scores (Table 3).

Table 3. Effect of treatment on the variables respiratory effort, accessory muscle use, wheezing, and Borg Dyspnea Scale score at hour 4.

Variable	Ciclesonide (n = 31)		Hydrocortisone (n = 27)		p	Relative effect size - OR (95% CI)
	N (%)	Absolute effect size (95% CI)	N (%)	Absolute effect size (95% CI)		
Respiratory effort	1(3)	32/1000	1(3)	28/1000	0.95	0.87 (0.05, 14.56)
Accessory muscle use	1 (3)	32/1000	2 (6)	28/1000	0.55	0.42 (0.04, 4.87)
Wheezing	8 (25)	258/1000	9 (31)	232/1000	0.55	0.70 (0.22, 2.16)
Borg $\geq$ 8	0 (0)	0/1000	0 (0)	0/1000	0.99	NE

m = mean; SD = standard deviation; CI = confidence interval; OR = odds ratio; NE= not estimable

Spirometric Variables. Both the patients treated with inhaled ciclesonide and those treated with hydrocortisone exhibited similar FVC, FEV1, and PEF values and a similar progression of these parameters. At hour 4, FVC and FEV1 values had not changed from baseline in either group. PEF increased significantly from baseline to hour 4 ($p < 0.001$) in both groups, and both treatments were equally effective when compared head-to-head at hour 4 (Table 4).

Table 4
Spirometric variables comparison of the two study treatments at hour 4.

Variable	Ciclesonide (n = 31)	Hydrocortisone (n = 27)	p	Absolute effect size (95% CI)
	m ± SD	m ± SD		
FVC	2.83 ± 0.99	2.67 ± 0.81	0.50	0.16 (-0.30, 0.62)
FEV1	1.82 ± 0.84	1.78 ± 0.61	0.83	0.04 (-0.30, 0.41)
PEF	276.89 ± 100.46	293.0 ± 92.24	0.51	-16,11 (-65.72, 33.50)
m = mean; SD = standard deviation; CI = confidence interval				
.				

Adverse Events. More patients in the hydrocortisone group complained of dry mouth, but there was no statistically significant difference in frequency of any adverse effect between groups (Table 5).

Table 5
Adverse events in both groups.

Ciclesonide (n = 31)				Hydrocortisone (n = 27)		
Event	n	%	95%CI	n	%	95%CI
Dry mouth	2	6.5	0 to 15.0	7	25.9	12.0 to 39.9
Palpitations	3	9.7	0 to 15.0	1	3.7	0 to 10.8
Tremors	11	35.5	0 to 37.4	7	25.9	12.0 to 39.6
Headache	2	6.5	0 to 15.0	3	11.1	10.4 to 11.8
Anxiety	1	3.2	3.0 to 3.4	2	7.4	0 to 17.3
There was no significant difference between groups; dry mouth was the only complaint more prevalent in the hydrocortisone group.						

Hospitalization, Losses, and exclusions. Two patients in the ciclesonide group developed worsening bronchospasm and severe desaturation still early in the course of treatment (having received only one dose of medication), and ultimately required ventilatory support.

Discussion

To the best of our knowledge, this was the first double-blind randomized clinical trial to test high-dose inhaled ciclesonide for the management of acute asthma in the emergency department. Our findings suggest that high-dose inhaled ciclesonide is as effective as intravenous hydrocortisone for this purpose. In this study, we tested ciclesonide as the intervention because it is a prodrug with high potency and minimal potential for side effects inhaled corticosteroid, which is particularly important for use in acute

exacerbations of asthma, a setting in which high doses of inhaled corticosteroids must be administered¹².

Studies have shown that inhaled and systemic corticosteroids can decrease the length of emergency department stay and hospitalization rate when administered the first hour of an acute asthma exacerbation¹⁶, but the optimal agent, dosage, and duration of observation in the emergency department are still unknown^{20,28}.

Both drugs reduced expiratory effort, wheezing, and accessory muscle use (Table 3); however, among the spirometric parameters analyzed, only PEF had improved significantly from baseline at hour 4 in both groups (Table 4). Adverse events, such as dry mouth, palpitations, tremor, headache, and anxiety, did not differ between the two groups (Table 5).

Clinical studies using high doses of inhaled corticosteroids such as fluticasone¹⁶, flunisolide¹⁷, and beclometasone¹¹ also found these agents to be effective in increasing peak flow.

Although we did not enroll a large number of patients, the groups did not differ in terms of demographic characteristics, except for the higher proportion of women in the ciclesonide group (Table 1). Two patients in the ciclesonide group, both with peak flow < 30% of predicted, developed worsening bronchospasm and severe desaturation still early in the course of treatment (having received only one dose of medication), and ultimately required invasive ventilation. Given the small sample, the likelihood of between-group differences is very high, and we judge these events to be attributable to chance.

Clinical parameters (Table 3) and vital signs (Table 2) were similar at baseline and at hour 4. Only DBP was higher in the hydrocortisone group, possibly due to the systemic effects of the corticosteroid³.

FVC and FEV1 remained unchanged from baseline to hour 4, and did not differ between the two groups. Previous studies of fluticasone¹⁶ and flunisolide¹⁷ reported improvement in these parameters. In our study, we observed an increase in PEF despite no increase in FEV1. This is consistent with the well-known mismatch between FEV1 and PEF in acute severe asthma^{29,30,31}, a condition in which FEV1 is underestimated and does not correlate adequately with rises in peak flow.

A Cochrane review noted the higher cost of inhaled versus systemic corticosteroids as an obstacle to use of the former²⁸. However, this was not an issue in our study, where 9 puffs of ciclesonide (total dose used in the emergency department) had an estimated cost of US\$2.47, while a single 500-mg dose of hydrocortisone had a cost of US\$3.18, making ciclesonide more cost-effective. In the United States, the average cost of treatment 30 days after a severe asthmatic exacerbation is US\$1368.32. Still regarding the cost and utility of inhaled corticosteroids, the FourFold Asthma Study (FAST) showed that it is clinically safe for a patient to simply quadruple their usual dose of inhaled corticosteroids at home upon deterioration, thus aborting a severe asthma attack and obviating the need for hospitalization³³.

Limitations of our study included the lack of follow-up (to assess for recurrence) and the small sample size, which, for instance, prevented us from determining whether dry mouth was truly more prevalent in the hydrocortisone group. Some strengths of our study include its design and external validity, since we included adult patients from general population with no restriction regarding to age, gender or ethnic group; rigorous evaluation of clinical and spirometric parameters; appropriate masking and blinding; and close, rigorous monitoring of patients for a 4-hour period during the study protocol.

Conclusion

In summary, our study suggests that high-dose inhaled ciclesonide is as effective as injectable hydrocortisone for the management of acute severe asthma and had a similarly favorable adverse-event profile, with the advantage of being a prodrug that exerts topical anti-inflammatory effects while reducing the risk of long-term systemic side effects.

Abbreviations

GINA

Global Initiative for Asthma

FEV1

Forced expiratory volume in the first second

AMA

Assistência Médica Ambulatorial

BMI

body mass index

PEF

peak expiratory flow

SBP

systolic blood pressure

DBP

diastolic blood pressure

HTN

hypertension

DM

diabetes mellitus

RR

respiratory rate

HR

heart rate

FVC

forced vital capacity

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Universidade Federal de São Paulo (# 364240). This study is registered in the Brazilian Registry of Clinical Trials (<http://www.ensaiosclinicos.gov.br/>) # RBR-6XWC26.

All patients provided written informed consent.

Consent for publication. In our study, all participants signed the consent form for participation in the study, authorizing the publication of results. The identification of the participants will be kept confidential.

Availability of data and material

Raw data are available in Supplementary 1 (ciclesonide group) and Supplementary 2 (hydrocortisone group).

Within-group analyses for ciclesonide and hydrocortisone can be found in Supplementary 3 (Tables A, B and C).

Competing interests

The authors declare that they have no competing interests.

Funding:

FAPESP – São Paulo Research Foundation: provided financial support for costs related to equipment maintenance, placebo preparation, logistic, patients public transport and feeding.

CNPq – National Council for Scientific and Technological Development: institutional research support.

CAPES – Coordination for the Improvement of Higher Education Personnel: institutional research support.

None of the above Government Institution participated in the research design, data acquisition, and neither were involved in data analysis or interpretation in any moment.

Author's contributions

DTM: study concept and design, acquisition of data, analysis and interpretation of data

KC: acquisition of data, analysis and interpretation of data

LBC: study concept and design, statistical analysis

LBFP: analysis and interpretation of data

CF: acquisition of data

GFP: study concept and design, analysis and interpretation of data, statistical analysis, critical revision of manuscript for intellectual content, and final approval of the version to be published.

All Authors have read and approved the manuscript.

Acknowledgements.

We acknowledge the full cooperation of the nurse staff from AMA Santa Cruz, AMA Heliópolis, and Hospital São Paulo. We also recognize the board of Directors of the Sociedade Paulista Para o Desenvolvimento da Medicina (SPDM) for their interest in academic activities.

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Figures

Figure 1

Flow Diagram of Patient Inclusion and Care

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