Evaluation of the Use of High-Dose Inhaled Corticosteroids for the Treatment of Acute Asthma

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Abstract

Introduction: Asthma is a heterogeneous disease characterized by chronic inflammation of the airways. It is characterized by certain respiratory symptoms such as wheezing, dyspnea, chest tightness, and cough that varies over time and in intensity, also showing variable airflow limitation. Asthma affects 1 to 18% of the world population.

Evidence suggests that inhaled corticosteroids may show early therapeutic effects (< 3 hours). This quick response would be linked to a topical effect (vessel constriction of the airway mucosa) due to the potentiation of the adrenergic effect by modifying the postsynaptic receptors.

Materials and Methods: A prospective, randomized, analytical and experimental longitudinal cohort study was performed in patients with asthma attacks treated at the emergency department of the Respiratory Rehabilitation Hospital "María Ferrer".

Results: A total of 71 patients were evaluated over a period of 10 months. All the patients were admitted through the emergency department of the Respiratory Rehabilitation Hospital "María Ferrer" after they had agreed to participate in the protocol by signing an informed consent.

Both groups had 63% of significant responses (Forced expiratory volume in first second, FEV1> 60%) 30 minutes after starting the treatment (p: 0.72). At the end of the protocol (180 minutes), three patients of the control group (salbutamol + ipratropium bromide) did not meet the $FEV_1 > 60\%$ objective, compared to 2 patients of the group treated with high-dose inhaled corticosteroids (p: 0.97).

Conclusion: Currently, the use of high-dose inhaled corticosteroids in asthma attacks is a therapeutic option for patients with mild to severe attacks. The results of our study do not provide significant evidence in support of the use of this medication to reduce the incidence of hospitalizations or to significantly improve the pulmonary function.

Key words: Asthma exacerbation, inhaled corticosteroid, FEV_1.

Introduction

Asthma is a heterogeneous disease characterized by chronic inflammation of the airways. It is characterized by certain respiratory symptoms such as wheezing, dyspnea, chest tightness and cough that varies over time and in intensity, also showing variable airflow limitation. Asthma affects 1 to 18% of the world population.

The objectives of the treatment of a patient having an asthma attack are: *a)* Correcting hypoxemia through oxygen administration (O_2), *b)* Relieving airflow obstruction through repeated administration of inhaled bronchodilators and *c)* Reducing inflammation and preventing relapses through the administration of systemic corticosteroids[2].

The evidence suggests that inhaled corticosteroids may show early therapeutic effects (< 3 hours)[3]. This quick response would be linked to the non-genomic effect of corticosteroids due to the potentiation of the adrenergic effect by modification of postsynaptic receptors[4].

To achieve maximum efficacy, inhaled corticosteroid administration should be made repeatedly,

together with beta-agonists. The work of Edmonds et al concludes that inhaled corticosteroids reduce hospitalizations, compared to placebo (OR [odds ratio] = 0.30; CI [confidence interval] of 95%, 0.16-0.57), but their benefits are not clear when compared to systemic corticosteroids[5].

Our objective is to evaluate bronchodilator response by adding high-dose inhaled corticosteroids to the usual salbutamol and ipratropium bromide treatment, both groups being under treatment with systemic corticosteroids.

Primary Objective

To compare the bronchodilator effect of salbutamol + ipratropium bromide in inhalation aerosol with salbutamol + ipratropium bromide + budesonide, all of them associated with systemic corticosteroids (IR bolus injection of dexamethasone 8 mg), and supplemental O_2 (if the transcutaneous oxygen saturation is < 90%) in patients who attend the emergency department of our hospital with mild to severe asthma attacks.

Secondary Objectives

To evaluate, in both treatment arms:
1. The increase of glycemia.
2. The variation in blood potassium.
3. The hospitalization rate.
4. The recovery hours until hospital discharge.

Materials and Methods

A prospective, randomized, analytical and experimental, comparative study. Comparisons of continuous variables were made with the t-test or the Mann-Whitney U test. The Kaplan-Meier method was used for time analysis, and the Log Rank Test was used for comparing treatments over time. The test results were considered significant for an alpha level $\alpha \leq 0.05$.

All the statistical analyses were done with the InfoStat statistical program, 2014 version. Faculty of Agricultural Science, National University of Córdoba. Some drawings were made with Excel Microsoft Office 2007.

Asthmatic patients aged $\geq$ 18 years who came to the emergency department of the María Ferrer hospital with mild to severe asthma attacks were included in the study.

Asthma attacks were considered as mild to severe if they presented a FEV_1 or peak espiratory flow (PEF) of less than 60% of the theoretical value, or ambient air O_2 saturation of less than 95%, and/or clinical signs of respiratory failure[6].

Patients were admitted in a numerical and consecutive way, the odd ones receiving the control group treatment with salbutamol (S) + ipratropium bromide (IB) (treatment 1), and the even ones receiving treatment with S + IB + budesonide (Bud) (treatment 2). Both groups received systemic corticosteroids at a dose of 8 mg of dexamethasone by intravenous route.

A few clinical examinations were performed, including the elements related to the current exacerbation. The following data was recorded: oxygen saturation, heart rate, spirometry with FEV_1 and peak-flow measurement, dyspnea level measurement (modified Medical Research Council [mMRC] scale), blood pressure and clinical evaluation of muscle retraction and wheezing.

We used: *Medix OXI-3* pulse oximeter, series number 1946, *Vitalograph ALPHA III* spirometer, 3-liter calibration syringe for spirometer with daily spirometer calibration, bronchodilator treatment including S + IB inhalation aerosol (100/21 mcg per dose), Bud inhalation aerosol (200 mcg/dose) and 8 mg ampoule of dexamethasone per intravenous route.

Oxygen was delivered with a nasal prong (if O_2 saturation was < 90%), and inhalation aerosols were applied with directly observed spacing chamber.

Forced spirometry was performed before starting the bronchodilator treatment and every 30 minutes until reaching 3 follow-up hours, with flow/volume curve printing and PEF measurement.

GROUP DESCRIPTION
Two groups:
1. Salbutamol + ipratropium bromide
2. Salbutamol + ipratropium bromide + budesonide

Salbutamol sulphate + ipratropium bromide in one inhalation aerosol (100/21 mcg per dose) with spacing chamber (making 7 respiratory cycles after taking each puff), at a total dose of 400/84 mcg (1 puff at a time) every 20 minutes within the first hour of treatment and then every 30 minutes until completing 3 hours of treatment and/or reaching 60% of the FEV_1 theoretical value.

Budesonide in inhalation aerosol (200 mcg per dose) with spacing chamber (making 7 respiratory cycles after taking each puff), at a total dose of 800 μgr (1 puff at a time) every 20 minutes within the first hour of treatment and then every 30 minutes until completing 3 hours of treatment and/or reaching 60% of the FEV_1 theoretical value.

Inclusion Criteria

1. Patients with mild to severe asthma attacks (worsening or acute exacerbation).
2. Patients shall sign the informed consent in order to perform the study.
3. Patients shall agree to a physical examination, spirometric evaluation and treatment.

Exclusion Criteria

1. Respiratory system disease (acute or chronic), such as acute community-acquired pneumonia, chronic obstructive pulmonary disease, pulmonary tuberculosis, cystic fibrosis, bronchiectases, diffuse interstitial pulmonary disease or other disease other than asthma attack.
2. Lack of cooperation on the part of the patient for the evaluation and treatment.
3. History of near-fatal asthma.
4. Smoking greater than or equal to 10 packs per year.
5. Glycemia record of $\geq$ 200 mg/dL in the first venous blood sample.
6. History of chronic renal failure.
7. Patients with special needs or patients who can´t read or write.
8. History of peripheral vascular disease that alters pulse O_2 saturation.

Results

The study was performed over a period of 10 months and evaluated a total of 71 patients. All the patients were admitted through the emergency department of the Respiratory Rehabilitation Hospital "María Ferrer" and agreed to participate in the protocol by signing an informed consent.

35 of the admitted patients also received inhaled corticosteroids; 47.9% were male, 45% were admitted with level 2 dyspnea, according to the mMRC scale, with a mean age of 43.7 years (+/-17.4) and FEV_1 mean values of 48.13% (+/-6.87) at admis-

sion. Both groups were comparable at the initial evaluation.

No significant changes were observed between the study groups, both of them being effective treatments, where 93% of patients reached more than 60% of the FEV_1 margin of safety within the first 3 follow-up hours (Table 1).

It was observed that 63% of the patients met discharge criteria within the first 30 minutes, with a mean improvement of 0.480 ml (+/- 0.333) measured by FEV_1, with no statistically significant values between both groups (p: 0.72).

Variations in blood potassium levels (Table 2) and pre- and post-treatment heart rate did not show significant changes, either. But, transcutaneous oxygen saturation showed significant differences between both groups after treatment, favoring the group treated with inhaled corticosteroids (p: 0.012), with a mean saturation of 97% and a FIO_2 (fraction of inspired oxygen) of 0.21 (Table 3). The difference between pre- and post-treatment glycemia was also significantly representative, with a p: 0.00001 value, but when both treatment arms were subdivided, the result did not show any statistically significant change favoring any of the groups (p: 0.9) (Tables 4, 5).

Discussion

In physiopathological terms, bronchial asthma is a disease that can be associated with inflammation of the airways and an increase in the local bloodstream[7]. This increase in blood perfusion comes from the bronchial arteries[8] and is distributed to
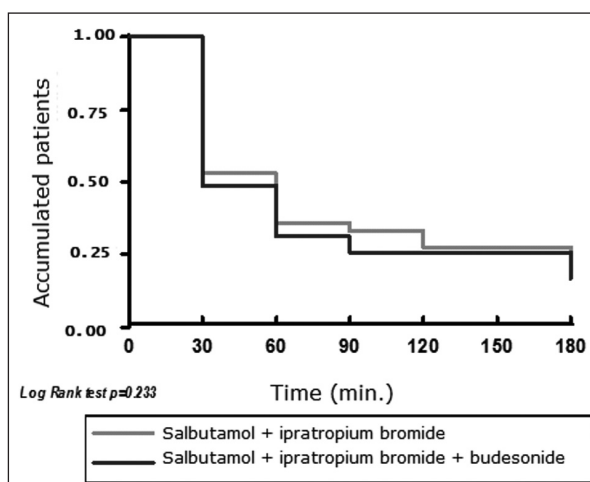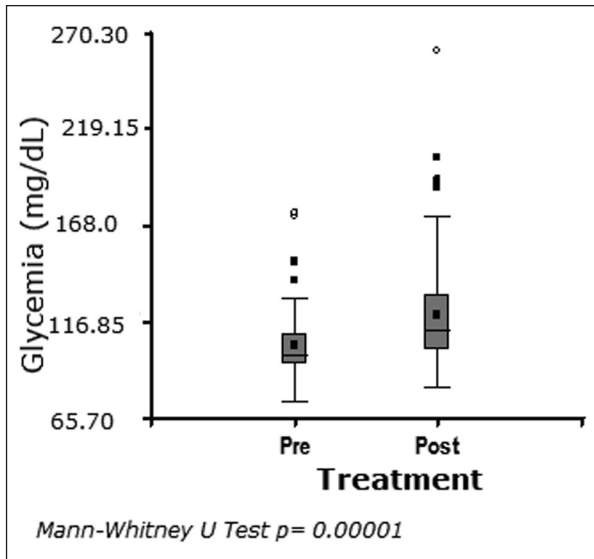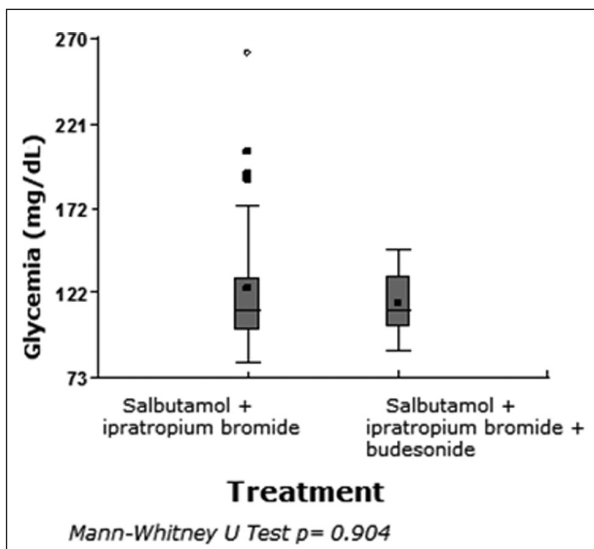

Log Rank test p=0.233

Table 1. Treatment and length of stay

Mann-Whitney U Test p= 0.00001

Moment	N	Range	Mean	SD	Median
Pre-treatment	71	75-175	103.83	18.210	99.00
Post-treatment	71	82-261	120.70	30.113	112.00
Total	142	75-261	112.27	26.201	105.00

Table 2. Pre- and post-treatment glycemia (mg/dL)

Mann-Whitney U Test p= 0.904

Glycemia (mg/dL)

Treatment	Mean	N	SD	Median
Salbutamol + ipratropium bromide	125.08	36	38.630	112.50
Salbutamol + ipratropium bromide + budesonide	116.20	35	17.017	112.00
Total		120.70	71	30.113	112.00

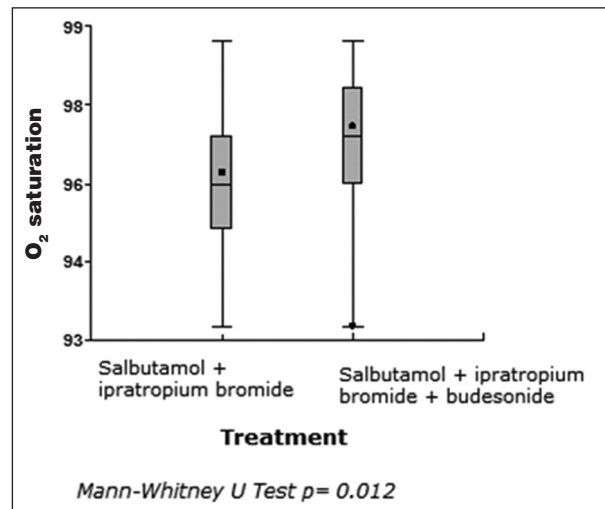**Table 3.** Glycemia (mg/dL) according to treatment

the subepithelial tissue. Inhaled corticosteroids are the first line treatment for mild to severe asthma[9].

Symptoms related to airflow limitation may be reduced spontaneously or after taking medication,

Mann-Whitney U Test p= 0.686

Blood potassium levels (mEq/L)

Treatment	Mean	N	SD	Median
Salbutamol + ipratropium bromide	3.897	36	0.4699	3.800
Salbutamol + ipratropium bromide + budesonide	3.840	35	0.3648	3.800
Total	3.869	71	0.4194	3.800

Table 4. Blood potassium levels (mEq/L) according to treatment

Mann-Whitney U Test p= 0.012

Treatment	N	Range	Mean	SD	Median
Salbutamol + ipratropium bromide	36	93-99	96.22	1.692	96.00
Salbutamol + ipratropium bromide + budesonide	35	93-99	97.20	1.568	97.00
Total	71	93-99	96.70	1.694	97.00

Table 5. O_2 saturation according to treatment

and even disappear for extended periods[1]. Despite the efficacy and safety of their current treatment, most patients are not thoroughly controlled.

Although some studies suggest a decrease in their morbidity and mortality, many patients still show exacerbations so severe that may put their lives at risk and require immediate attention at the emergency department[7].

The guidelines of the Global Initiative for Asthma (GINA) define an asthma attack as acute or subacute worsening of the symptoms and pulmonary function of the patient with asthma that modify his/her baseline condition and that in some cases may be the first expression of the disease in a patient with no previous diagnosis of asthma[1].

Asthma attack is a frequent reason for consultation in the emergency department[10]. Approximately 15 to 25% of patients who come to the emergency department may require hospitalization, and 10 to 20% of the patients who are discharged from the emergency department will relapse within the following 2 weeks[11].

Rodrigo et al showed that the administration of inhaled drugs is the method of choice for the treatment of acute asthma, since it is associated with a faster onset of action and less side effects, as a consequence of the low doses that are required to obtain the therapeutic effect at the airways and the fact that some drugs are poorly absorbed into the bloodstream[2, 12, 13].

One of the most important factors for the efficacy of the bronchodilator treatment is the inhalation maneuver for drug administration and the puff-inspiration coordination. There may be up to 80% oropharyngeal deposition of the dose as a consequence of a wrong inhalation maneuver. This has been partially solved with the introduction of one-way valve inhalation chambers placed between the metered-dose pressurized inhaler (MDPI) and the patient, reducing the oropharyngeal deposition (10-15 times), with less side effects. The use of these devices increases the amount of administered drug that reaches the lungs, though not as much as it reduces the oropharyngeal deposition (since many particles are deposited in the walls of the inhalation chamber), and reduces the treatment time[14].

In our study we used inhalation spacing chambers, since we could not obtain single-valve chambers. This way we make sure an effective dose of the bronchodilator treatment is administered and an adequate maneuver observed by experts is performed, avoiding any mistake due to a wrong management.

Currently there are very few studies that assess the use of inhaled corticosteroids for the treatment of asthma attacks. Marcia L et al made a meta-analysis about the use of inhaled corticosteroids at the emergency department for asthma attacks.

The inclusion criteria for this meta-analysis included studies comparing the use of inhaled corticosteroids (IC) with placebo without using systemic corticosteroids, and other studies comparing the use of IC with placebo plus the administration of systemic corticosteroids to both groups. 5 of the studies of the meta-analysis that reported hospitalizations showed a significant reduction of hospital admissions in the group treated with inhaled corticosteroids, (OR [odds ratio] 0.30; CI [confidence interval] of 95%, 0.16 to 0.57) with no heterogeneity between the assessed studies, but showed that 1 hospitalization was avoided every 6 treated patients. The studies assessing the pulmonary function showed a benefit in favor of the use of inhaled corticosteroids, but without any statistically significant values (p=0.15)[15].

Edmond et al carried out a recent Cochrane review showing the reduction in the hospitalization rate within the group of patients treated with inhaled corticosteroids for asthma attack symptoms, but the studies assessed in this review use patients who are compared to placebo or systemic corticosteroids, none of them with fast-acting B_2 agonists[16].

Another evidence-based review was presented by Rodrigo, showing a lower hospitalization rate, a shorter length of stay at the emergency department and a very good FEV_1 response in patients who received high-dose inhaled corticosteroids during the first hours of emergency care at the emergency department; but it should be made clear that most of the studies included in this review compare this effect with placebo or systemic corticosteroids and not with the conventional, standardized aerosol bronchodilator treatment[17], as in our study.

During our study, we did not observe a better bronchodilator response in terms of the FEV_1 or a lower hospitalization incidence within the group of patients treated with high-dose inhaled corticosteroids.

Both groups had 63% of significant responses ($FEV_1 > 60\%$) 30 minutes after starting the treatment (p: 0.72). At the end of the protocol (180 minutes), the control group (S + IB) presented 3 patients who did not meet the $FEV_1 > 60\%$ objective, compared to 2 patients of the group treated with high-dose inhaled corticosteroids (p: 0.97).

Clinical and spirometric improvement in both groups was remarkable within the first 60 minutes

after starting the treatment. We believe one of the most important factors influencing this quick response was the administration of a controlled treatment observed by experts with MDPI through a spacing chamber. This suggests, for future studies, the possibility of obtaining a lower cost and a greater benefit both for the asthmatic population and for our hospital.

The hyperglycemia observed after administrating systemic glucocorticosteroids compels us to provide extra monitoring of patients at risk.

Neither the blood potassium levels nor the heart rate showed any significant changes after treatment with fast-acting Beta 2 agonists. This could be a consequence of the little exposure time most of the patients had, since more than 50% were discharged within the first 60 minutes after starting the treatment.

Conclusion

Our study did not obtain statistically significant values that support the addition of high-dose inhaled corticosteroids to the conventional treatment in patients with asthma attacks.

An equally important issue was finding early recovery in patients who received directly observed treatment. This raises questions about the cost/effectiveness of the length of stay of these patients "under hospital roof", in the emergency department.

We believe more studies are needed to assess such response and evaluate its effectiveness at reducing the hospitalization rate and also at being objectively assessed in spirometric values.

Conflicts of Interest: The authors declare there is no conflict of interest related to this publication.

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