Prednisone in COPD exacerbation requiring ventilatory support:
An open-label randomised evaluation

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**Running head:** Systemic steroids in acute exacerbation of COPD

**Study message:** In COPD exacerbation requiring ventilatory support, Prednisone has no impact on ICU mortality or related patient-centred outcomes.

This study is registered with clinicaltrials.gov number: NCT01353235

**Author contribution:**
FA designed the study, contributed to analysis, and wrote the first draft of the paper with input from all other authors. LOB, LB and SE participated in study conception and design, data analysis, and finalising the report. MFH, SA, IO and FD participated in acquisition of data and drafting of the report. All authors revised the report and have seen and approved the final report.
Abstract:

Background: Recommendations of systemic steroids in COPD exacerbation rely on trials that excluded patients requiring ventilatory support.

Methods: in an open-label, randomised evaluation of oral prednisone administration, 217 patients with acute COPD exacerbation requiring ventilatory support were randomised (with stratification on the type of ventilation) to usual care (n=106), or to receive a daily dose of prednisone (1mg/kg) for up to 10 days (n=111).

Results: There was no difference regarding the primary end-point, in-ICU mortality: 17 deaths (15.3%) vs 15 deaths (14%), in steroid treated and in control groups, respectively (Relative risk: 1.08, 95%CI: 0.6-2.05). Analysis according to ventilation modalities showed similar mortality rates. NIV failed in 15.7% and 12.7% (RR: 1.25, 95%CI: 0.56-2.8, p=0.59), respectively. Both study groups had similar median mechanical ventilation duration, and ICU length of stay: 6 (3-12) days vs 6 (3.8-12), and 9 (6-14) vs 8 (6-14), respectively. Hyperglycaemic episodes requiring initiation or alteration of current insulin doses occurred in 55 patients (49.5%) vs 35 patients (33%) in prednisone and control groups, respectively (RR: 1.5, 95%CI: 1.08-2.08; p=0.015).

Conclusions: Prednisone did not improve ICU mortality or patient-centred outcomes in the selected subgroup of COPD patients with severe exacerbation. It significantly increased the risk of hyperglycaemia.

Key words: acute respiratory failure, COPD, COPD exacerbation, mechanical ventilation, steroids.
**Introduction:**

Chronic obstructive pulmonary disease (COPD) is a condition of chronic airflow limitation that is not completely reversible and is often progressive[1]. It has become by 2010, the third leading cause of mortality worldwide [2]. The natural course of COPD is characterised by the occurrence of exacerbations (usually 2-3 per year) requiring an emergency visit, or hospitalisation [3-5]. Acute exacerbations of COPD (AECOPD) are not only responsible for the most part of economic burden associated with COPD, they also accelerate the lung function decline and worsen the prognosis of the disease with an elevated in-hospital and one year mortality (11% and 40%, respectively), and a six-month relapse rate of 50% [6-10]. COPD exacerbations are usually associated with increases in local and systemic inflammatory response, and are treated with systemic steroids in accordance with high grade recommendations [3, 11-13]. Indeed, although data are insufficient to define the optimal dose, route or duration of systemic corticosteroids, current guidelines strongly recommend administration of systemic steroids (prednisone equivalent doses of 30 to 40 mg/d) to hospitalised patients with AECOPD [1, 14, 15]. Recommendations rely on meta-analyses with cumulated effects showing both significant reduction in the rate of treatment failure, and an increase in the rate of improvement in lung function, and dyspnoea [16-18]. However, systemic corticosteroids were not associated with a reduction in the mortality rate, and induced a significant increase in adverse effects (in particular a five-fold increase in hyperglycaemic episodes) [17, 18]. Moreover, primary studies included in these meta-analyses usually excluded COPD patients with exacerbation severe enough to require ventilatory support in the Intensive Care Unit (ICU). It is therefore unclear whether recommendations derived from studies that systematically excluded patients with severe AECOPD requiring ventilatory support, should be extrapolated to this type of patients especially knowing that corticosteroid administration to critically ill patients might be associated with severe adverse events such as infections, muscle paresis, hyperglycaemia and other metabolic disorders. These side effects entail increased morbidity and mortality. In the particular COPD population, hyperglycaemic episodes were clearly associated with poor outcomes with an increased rate of non invasive ventilation failure[19, 20].
In this context of evidence paucity, Alia et al have recently published the only study dealing specifically with patients suffering from severe COPD exacerbation requiring ventilatory support [21]. This multicenter Spanish randomised study included 83 patients and evaluated the effects of a 10-day course of intravenous methylprednisolone. Compared to placebo, corticosteroids reduced by one day the duration of mechanical ventilation, and reduced by 93% the risk of failure of non-invasive ventilation. Conversely, steroid treatment had no impact on ICU mortality, and induced a two-fold increase in hyperglycaemic episodes.

The current study reports a prospective, open-label, randomised evaluation of oral prednisone administration in acute COPD exacerbation requiring ventilatory support.

**Methods:**

This randomised controlled trial with 2 parallel groups was conducted between 2008 and 2011 in two Tunisian ICUs belonging to two tertiary teaching hospitals: CHU Fattouma Bourguiba, Monastir and CHU Tahar Sfar, Mahdia, both of which affiliated with the University of Monastir. The trial was approved by the ethics committee of both participating centres, and written informed consent was obtained from the patients or their surrogates.

**Inclusion criteria:** all patients aged 40 years or older, with a history of at least 10 pack-year of cigarettes smoking, and with known or strongly suspected COPD, who were admitted to participating ICUs for an acute COPD exacerbation with hypercapnic acute respiratory failure requiring ventilatory support, were considered for inclusion in the study. COPD, COPD exacerbation, and respiratory failure were defined according to the Global Strategy for the Diagnosis, Management and Prevention of COPD[1]. COPD is defined as a preventable and treatable disease whose pulmonary component is characterised by airflow limitation that is not fully reversible. Airflow limitation was deemed present if the post-bronchodilator ratio of FEV1/FVC ratio was less than 0.7. Patients with suspected COPD and without previous documentation of FEV1/FVC ratio, had pulmonary function tests checked upon ICU discharge. COPD exacerbation corresponds to a change in patient’s baseline dyspnoea, cough, and/or sputum requiring a change in regular medication. Acute respiratory failure is defined by a severe hypoxemia (PaO2<60mmHg and/or SaO2<90% on room air) associated with hypercapnia (with PaCO2 ≥45mmHg associated with pH ≤ 7.35) and clinical signs of
excessive respiratory muscle activity (contraction of accessory respiratory muscles, Respiration rate ≥25 breaths/min.).

**Non Inclusion criteria:** patients were not included if they had evidence of pneumonia, were treated for COPD exacerbation with systemic steroids within 30 days before screening, or had an absolute contra-indication to steroids (active gastro-duodenal ulcer, severe uncontrolled sepsis, hepatitis or other active viral disease, neuromuscular disease).

**Protocol:** In addition to ventilatory support, all included patients received nebulisation of β2 agonists (terbutaline, 5 mg every 6 hours) and ipratropium bromide (0.5 mg every 8 hours). Antibiotics were prescribed at the discretion of physician in charge. Patients were randomised (by means of sealed envelopes that were opened sequentially), to receive prednisone as an add-on therapy to usual treatment. Randomisation was performed at each centre by a random number table, and was stratified according to the type of mechanical ventilation (conventional or non-invasive, NIV). Patients assigned to corticosteroid treatment arm, received oral prednisone 1mg/kg, daily until discharge or for a maximum of 10 days. Prednisone was administered within 24 hours after ICU admission, as a single dose in the morning. In patients on conventional mechanical ventilation, the tablets were administered by feeding tube.

In patients who were initially treated with non-invasive ventilation, NIV was deemed failing (and patients considered to need tracheal intubation) if any of the following major criteria was present: hypercapnia with respiratory acidosis (pH ≤7.20 and below its value at inclusion); hypercapnic coma (Glasgow Coma Scale 8 and PaCO2 ≥ 60 mm Hg); PaO2 of less than 45 mm Hg despite a maximum tolerated fraction of inspired oxygen; and/or cardiac arrest. In intubated patients, weaning from mechanical ventilation was started after daily screening to evaluate their recovery from respiratory failure and their eligibility to the weaning process. Patients were considered ready to be weaned from MV when they met the following weaning criteria: PaO2/FiO2≥150 mmHg; an effective cough; no vasopressors nor sedation, and a Glasgow Coma Score≥12. Weaning started with an SBT on a T-tube for 2 hours. Patients who tolerated the SBT trial were subsequently extubated. SBT was deemed failing when any of the following signs of intolerance was present: agitation, altered neurological status, cyanosis, contraction of accessory respiratory muscles, thoraco-abdominal dyssynchrony, tachypnea, tachycardia, or arrhythmia.
Noninvasive ventilation was considered successful and stopped if the initial NIV criteria were no longer present while breathing without ventilatory assistance for at least 4 hours.

Endpoints: The primary endpoint was ICU mortality. The secondary endpoints were the lengths of ventilatory support (the sum of conventional and non invasive ventilation in those ventilated with both), and that of ICU stay. The rate of NIV failure (inferred from the intubation rate in patients managed initially with NIV) was also compared between study groups. Corticosteroids complications were evaluated on the occurrence of secondary infections, hyperglycaemic episodes necessitating initiation of insulin therapy (corresponding to a blood glucose level ≥180mg/dl in patients without pre-existing diabetes) or increase in initial insulin therapy, ICU-acquired muscular weakness, or significant gastro-intestinal bleeding inducing a fall in the haemoglobin level ≥2g/dl.

Statistical analyses: Data are presented as medians (Interquartile range, IQR), or proportions, as appropriate. The study groups were compared on an intention-to-treat basis, and P≤.05 was considered significant. Continuous variables were compared with the Mann-Whitney test. Categorical variables, were compared with Chi² test. Based on the mortality rate we previously reported in this type of patients (22% in the control group), we calculated that it would be necessary to include 150 patients in each arm of the study in order to detect 12% reduction in the absolute risk of mortality with a power of 80% and a two-tailed alpha risk at 0.05[22]. SPSS version 17 software package (Chicago,IL, USA) was used for statistical analyses.

Results:
During the study period, 518 patients were admitted in both participating ICUs for severe COPD exacerbation requiring ventilatory support. Of these, 217 (42%) fulfilled the inclusion criteria and were included in the study and randomised to active treatment group (n=111) or to control group (n=106). The study was ended before completion of the planned sample size because of the slow inclusion rate. The study flow chart is reported in Figure 1. The main cause of non inclusion was treatment with systemic corticosteroids within the preceding 30 days, or the presence of pneumonia as a cause of exacerbation. There was no difference in baseline characteristics of included and non included patients, in particular with regard to age, SAPSII, and pH.
Baseline characteristics of both study groups are reported in table I. Treatment and control groups were similar with respect to demographics, COPD severity (70% and 73% of GOLD stage IV, respectively), the frequency of comorbidities, and the severity of acute exacerbation as reflected by SAPSII [29 (24-35) vs 27 (20-35)], and pH: 7.28(7.25-7.32) vs 7.29 (7.25-7.32), respectively.

Similar rates of NIV (76%) were applied as initial ventilation mode in both groups. Prednisone was administered for a median of 8 (IQR: 5-10) days in the active treatment group. Its administration started at a median of 9 (IQR: 6-13) hours, following the admission to the ICU. All patients received nebulised terbutaline, and ipratropium. The use of systemic antibiotics was no statistically different: antibiotics (mainly cephalosporins in association with either one quinolone or macrolide) were administered in 82% and 79% in the steroids and control groups, respectively, and for a median duration of 7 days.

**Outcomes:** there was no statistically significant difference between patients treated with prednisone and the control group with regard to the main end-point namely mortality in the ICU (table II): 17 deaths (15.3%) vs 15 deaths (14%), respectively; Relative risk: 1.08, 95% CI: 0.6-2.05; p=0.81). Similar mortality rates were also found in non-invasively ventilated patients: 10.5% vs 11%, (RR: 0.93, 95% CI: 0.37-2.35; p=0.88) in treated and control groups, respectively. In the subgroup of patients who had conventional ventilation ICU mortality occurred in 25.7% and 20% in the prednisone and control group respectively: RR: 1.28, 95% CI: 0.54-3; p=0.57.

NIV failed in 12 patients (15.7%) and 9 patients (12.7%) in treated and control groups respectively (RR: 1.25, 95%CI: 0.56-2.8, p=0.59). None of the study patients was intubated due to cardiac arrest. Both study arms had similar mechanical ventilation duration, and ICU length of stay: 6 (4-12) days vs 6 (3.8-12), and 9 (6-14) vs 8 (6-14), respectively.

No episode of ICU-acquired muscle weakness, or gastro-intestinal bleeding occurred in the study population. Ventilator associated pneumonia episodes occurred in 5 and 4 patients in the prednisone and control groups, respectively. Hyperglycemic episodes requiring initiation or alteration of current insulin doses occurred in 55 patients (49.5%) vs 35 patients (33%) in prednisone and control groups, respectively (RR: 1.5, 95%CI: 1.08-2.08; p=0.015).
Discussion:

In this prospective open-label controlled study, the evaluated regimen of oral prednisone (1mg/Kg daily for up to 10 days) in patients admitted to the ICU for COPD exacerbation requiring ventilatory support, had no effects on patient-centred outcomes such as in-ICU mortality, mechanical ventilation duration, length of ICU stay, or the rate of non-invasive ventilation failure. Prednisone administration was associated with a significant increase in the rate of hyperglycaemic episodes requiring initiation or alteration of current insulin treatment. Given the established evidence on the negative impact of hyperglycaemic episodes on the outcome of critically ill patients in general, and in particular those admitted for acute COPD exacerbation, our study does not argue for the systematic administration of corticosteroids in severe COPD exacerbation requiring ICU admission and ventilatory support.

The present study was stopped before its completion because of a slow inclusion rate. Although it achieved 70% power to detect the 12% assigned lowering in the absolute risk of ICU mortality, the current study was underpowered and should not be considered a definitive negative study. Indeed, the lower boundary of the confidence interval for the effect on mortality can not preclude a lowering by 40% in the relative risk of ICU mortality. According to the mortality rate observed herein, a prospective randomised trial would take no less than 2000 patients to detect the minimum clinically important reduction in mortality and draw definitive conclusion regarding the effects of systemic corticosteroids on mortality. Similar numbers are also needed for the evaluation of another patient centred outcome such as non-invasive ventilation failure. The open-label design of an RCT may elicit bias in reporting potential endpoints. However, the fact that our study focused on the so-called “hard” endpoints, increases confidence in observed results. Notwithstanding these limitations, the results of our study actually challenge the findings of Alia et al, and the explicit recommendations of systematic administration of systemic steroids in COPD exacerbation [4, 11, 21]. Regarding patients admitted in ICUs, most of these recommendations could be regarded as not fully supported since they rely on studies that explicitly excluded patients requiring ICU admission and ventilatory support [14, 17, 23, 24].
The only available study that dealt specifically with patients requiring ventilatory support, has recently been published by Alia et al who conducted a multicenter double-blind placebo-controlled trial evaluating a 10-day course of intravenous methylprednisolone in patients with severe COPD exacerbation [21]. Patients were randomised to receive either intravenous methylprednisolone (2 mg/Kg for 3 days, 1 mg/Kg for the following 3 days, then 0.5 mg/Kg for the remaining 4 days), or placebo. The main outcome measure was the mechanical ventilation (MV) duration, and a sample size of 198 patients was deemed necessary in order to reduce MV duration by 2 days. Owing to a low inclusion rate precluding the study completion, only 83 patients were eventually included in the trial (43 in the active treatment group, and 40 in the placebo group). Still, the authors reported a small but statistically significant reduction by one day in the MV duration (from 4 days in the control group to 3 in the steroid group). Steroid treatment only marginally impacted both the ICU mortality and the length of stay. The most striking effect of steroid treatment in this study was observed among the subgroup of 37 patients who received NIV with a reduction in the NIV failure rate: 0 out of 18 in the steroid treatment group compared to 7/19 (37%, RR: 0.07) in the control group. Although this effect seems clinically relevant, the small number of patients in whom this was observed, should make one cautious in interpreting these results, which deserve further confirmation. NIV was indeed used as a first ventilatory mode in only 44% compared to 76% in our study.

The apparent contradiction between our results and those of Alia et al should not be readily explained by the difference in the chosen scheme of steroid administration. Only differences pertaining to the initial corticoid dose and administration route, could actually be considered relevant, and might account for the apparently discrepant results. In the study by Alia et al, patients received (during the first 3 days, by the intravenous route) a prednisone equivalent dose twice that received by our patients. However, issues like steroid daily dose, the route of administration, the course duration are poorly standardised in the treatment of COPD exacerbation. Different doses (low initial dose vs higher doses) [18], route of administration (PO or iv) [25, 26], and course durations (3 days, 7 days, or even beyond) [27], have been used in previous studies, and little evidence if any, suggest that these parameters could have a drastic impact on steroids efficacy. For the particular issue of initial steroid dose, a meta-analytic comparison of high initial dose (ie ≥80 mg prednisone equivalent dose) and low initial dose of systemic steroids, showed no superiority of the high dose regimen over
the low dose regimen[18]. With regard to these considerations, we do not see a major design difference between our study and that of Alia et al, and potential causes of differences, including the effect on NIV failure, must be sought elsewhere. As acknowledged by the authors, the fact that NIV failed in none of the 18 NIV ventilated patients from the steroid group accounted for a greater impact on MV duration in the NIV subgroup (minus 2 days in MV duration in this subgroup), and could explain the statistically significant reduction by one day of the MV duration in the overall population. In fact, NIV failure rates reported by Alia et al, either the one observed in the control group (37%) or that recorded in the intervention group (0%), are very dissimilar to the average (16%) reported so far in the literature [28]. As a matter of fact, the impact of steroid treatment on the NIV failure rate might suggest that despite randomisation, two populations with different inflammatory and biological characteristics were actually included in each study arm in the RCT by Alia et al [21]. AECOPD is indeed heterogeneous with respect to inflammation, which is most often predominantly neutrophilic but can be eosinophilic in a significant number of instances [29, 30]. Patients with eosinophilic inflammation behave merely like asthmatic patients, with a strong expression in bronchospastic exacerbations, and a high potential for reversibility under corticosteroid treatment. Clinically, these patients are very difficult to distinguish from others at the time of exacerbation. Auscultation of wheezing only reflects bronchial obstruction and does not indicate its potential for reversibility. The measurement of FEV1 and a reversibility test under inhalation of bronchodilators, is virtually impossible to perform in such dyspneic patients. Some studies have shown that sputum eosinophilia can predict a positive response to corticosteroids treatment in stable COPD or can be used to titrate maintenance steroid treatment [31-33]. The eosinophilic pattern of inflammation in COPD exacerbation is also reflected by an increase in peripheral blood eosinophil count [30], and Bafadhel et al have recently validated the use of peripheral blood eosinophil count to guide systemic corticosteroids prescription during AECOPD [34]. The different results of the study by Alia et al and our study suggest that different subpopulations were enrolled and one may hypothesize that a strategy of corticosteroid prescribing based on peripheral blood or sputum eosinophil count might be an interesting approach, considering the risk-benefit balance in this population. Testing such an approach could help to better determine a specific subpopulation of patients with COPD exacerbation who could benefit from systemic corticosteroids.
Even if the level of statistical significance was not achieved, the effects of steroid administration on the primary outcome that is ICU mortality, seem quite different in patients ventilated non-invasively (RR=0.93) compared to the intubated population where the relative risk of ICU mortality is increased by 28% (RR=1.28). We cannot readily account for these statistical trends, but we can speculate that in intubated patients, systemic steroids may alter general prognosis either by favoring ventilator associated pneumonia, or by inducing a higher rate of hyperglycemic episodes. The reduced sample of the subgroup of intubated patients in our study precludes such post-hoc analysis, which has anyway a limited scientific value.

We see no impediment or bias that could prevent the extrapolation of the results of this two-center study to other patients/settings. The clinical characteristics, management, and outcomes of the patients included herein are similar to those generally reported in severe exacerbation of COPD requiring ICU admission and ventilatory support. This is in particular seen through the severity of the index episode (inferred from median SAPS and pH at inclusion), the rates of NIV use and failure, and that of mortality which are in the levels usually reported in studies dealing with severe COPD exacerbation[21, 35-38].

In sum, administration of steroids in patients with severe episodes of COPD exacerbation and requiring ventilatory support, failed to demonstrate any benefit, did not alter the rate of noninvasive ventilation failure and resulted in more frequent episodes of hyperglycemia. These results do not support recommending this approach until a more precise identification of potential responders is possible.
Table I: Baseline characteristics of the study patients

<table>
<thead>
<tr>
<th></th>
<th>Prednisone (n=111)</th>
<th>Control (n=106)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>70 (63-75)</td>
<td>68 (63-75)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>99 (89)</td>
<td>92 (87)</td>
</tr>
<tr>
<td>Baseline FEV1, (ml/s)</td>
<td>820 (590-1120)</td>
<td>750 (565-950)</td>
</tr>
<tr>
<td>COPD duration, years</td>
<td>10 (5-12)</td>
<td>8 (5-12.5)</td>
</tr>
<tr>
<td>Home oxygenotherapy, N° (%)</td>
<td>80 (72)</td>
<td>71 (67)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Diabetes N°, (%)</td>
<td>17 (15)</td>
<td>13 (12)</td>
</tr>
<tr>
<td>History of Hypertension N°, (%)</td>
<td>9 (8)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>History of heart failure N°, (%)</td>
<td>14 (13)</td>
<td>13 (12)</td>
</tr>
<tr>
<td>GOLD stage, N° (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>33 (30)</td>
<td>29 (27)</td>
</tr>
<tr>
<td>IV</td>
<td>78 (70)</td>
<td>77 (73)</td>
</tr>
<tr>
<td>Cause of AECOPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Tract infection</td>
<td>50 (45)</td>
<td>46 (43)</td>
</tr>
<tr>
<td>Heart dysfunction</td>
<td>34 (31)</td>
<td>32 (30)</td>
</tr>
<tr>
<td>Unidentified</td>
<td>27 (24)</td>
<td>28 (27)</td>
</tr>
<tr>
<td>SAPSII</td>
<td>29 (24-35)</td>
<td>27 (20-35)</td>
</tr>
<tr>
<td>Respiratory rate, (breaths/min)</td>
<td>30 (25-34)</td>
<td>29 (24-34)</td>
</tr>
<tr>
<td>Arterial Blood Gases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.28 (7.25-7.32)</td>
<td>7.29 (7.25-7.32)</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>78 (62-85)</td>
<td>80 (62-87)</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>90 (84-94)</td>
<td>89 (83-94)</td>
</tr>
<tr>
<td>CRP mg/l</td>
<td>24 (12-57)</td>
<td>37 (12-66)</td>
</tr>
<tr>
<td>Initial ventilatory support N°, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIV, N° (%)</td>
<td>84 (76)</td>
<td>80 (76)</td>
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<tr>
<td>-----------</td>
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</tr>
<tr>
<td>Conventional, N° (%)</td>
<td>27 (24)</td>
<td>26 (24)</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range), unless otherwise stated.

Définition of abbreviations: CRP= C Reactive Protein, GOLD= Global Initiative for Chronic Obstructive Lung Disease, SAPSII: Simplified Acute Physiology Score II, NIV = non invasive ventilation,
### Table II: Efficacy and safety endpoints

<table>
<thead>
<tr>
<th></th>
<th>Prednisone group</th>
<th>Control group</th>
<th>Relative risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy endpoint</strong></td>
<td></td>
<td></td>
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<tr>
<td>ICU mortality</td>
<td>17/111 (15.3%)</td>
<td>15/106 (14%)</td>
<td>1.08 (0.6-2.05)</td>
<td>0.81</td>
</tr>
<tr>
<td>ICU mortality in patients</td>
<td>8/76 (10.5%)</td>
<td>8/71 (11%)</td>
<td>0.93 (0.37-2.35)</td>
<td>0.88</td>
</tr>
<tr>
<td>ventilated with NIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU mortality in patients</td>
<td>9/35 (25.7%)</td>
<td>7/35 (20%)</td>
<td>1.28 (0.54-3)</td>
<td>0.57</td>
</tr>
<tr>
<td>ventilated conventionally</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NIV failure</td>
<td>12/76 (15.7%)</td>
<td>9/71 (12.7%)</td>
<td>1.25 (0.56-2.8)</td>
<td>0.59</td>
</tr>
<tr>
<td>Mechanical ventilation duration (days)</td>
<td>6 (4-12)</td>
<td>6 (3.8-12)</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>9 (6-14)</td>
<td>8 (6-14)</td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Safety endpoint</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hyperglycemic episodes</td>
<td>55/111 (49.5%)</td>
<td>35/106 (33%)</td>
<td>1.5 (1.08-2.08)</td>
<td>0.015</td>
</tr>
<tr>
<td>requiring initiation or alteration of insulin therapy</td>
<td></td>
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</tbody>
</table>

Définition of abbreviations: ICU = intensive care unit, NIV= non invasive ventilation
Figure 1: Flow chart

Screened for eligibility

518

Excluded: 301

- 160 Steroid treatment
- 74 Pneumonia
- 32 Pulmonary embolism
- 19 Pneumothorax
- 16 Refused consent

Included in the study

217

Prednisone Group

111

Control Group

106

Non Invasive Ventilation

- 84

Conventional mechanical ventilation

- 27

- 80

- 30
References:


