Study protocol

High-flow Nasal Oxygen versus Non-invasive CPAP Ventilation Support for Hypercapnic Respiratory Failure (The HIGH-for-HYPER study)

Study group

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Background

Hypercapnic respiratory failure

Respiratory failure is a leading cause of morbidity and mortality, and one of the most frequently encountered problems at the emergency department[1,2,3].

Hypercapnic or hypercarbic respiratory failure, also dubbed respiratory failure type II, is characterized by failure of the respiratory system in one of its two gas exchange functions: carbon monoxide (CO_2) elimination. It is thus usually defined via partial pressure of CO_2 in the arterial blood gas ($PaCO_2$), a value of higher than 50mmHg being a commonly used cut-off[4,5].

Hypercapnic respiratory failure is often associated with severe airway disorders, such as asthma and chronic obstructive pulmonary disease (COPD), but might also be found in other situations, where respiratory drive is restricted, such as intoxications, neuromuscular diseases or chest wall abnormities[4,5].

Hypercapnic respiratory failure, i.e. respiratory failure type II, is often associated with hypoxemic respiratory failure, i.e. respiratory failure type I, failure of oxygenation, however type I failure is also often observed without hypercapnia[4,5].

Respiratory failure, both type I and II, may be further classified into either acute or chronic. Distinction between both forms is often not easy, and, in addition to arterial blood gas analysis, might require additional tests to identify clinical markers such as polycythemia or cor pulmonale. For practical reasons, acute respiratory failure is often defined as a situation, in which respiratory failure develops too fast to allow for renal compensation and an increase in bicarbonate (HCO_3^-) levels, and thus leading to acidosis (pH less than 7.3)[4,5].

Therapy strategies for hypercapnic respiratory failure include non-invasive CPAP ventilation support, intubation and mechanical ventilation (both assisted and controlled forms)[4,5], and, in very severe cases, extracorporal methods, such as extracorporal life support systems[6,7].

Non-invasive CPAP Ventilation Support

Non-invasive CPAP ventilation support via either helmets, or different kinds of tight masks, is the current method of choice for the treatment of patients with acute respiratory failure in the intensive care setting. Eligible patients include those with an intact airway, airway-protective reflexes, who are alert enough to follow commands, whereas patients who lack those criteria require immediate intubation[4,5].

Non-invasive CPAP ventilation support improves both oxygenation (by providing an inspired fraction of oygen (FiO^2) of 100%, which is not possible via a simple venturi-mask, and the possibility of positive end-expiratory pressure (PEEP), preventing collapsing of the alveoli), and decarboxygenation (by increasing tidal volume). It has been shown to decrease both need for intubation and in-hospital mortality[8].

Non-invasive CPAP ventilation support however requires a high grade of skill from providers, and intensive communication with the patient to explain to him the usefulness of a tight-sitting device in his face in a situation of perceived massive dyspnea. Although severe adverse effects of non-invasive CPAP ventilation support are very rare, pain and pressure marks may occur. Despite all efforts of care providers, there is a relevant faction of patients who do not tolerate ventilation support via a tight mask at all. Brochard et al. report 15% of patients not tolerating the therapy, with an additional 25% of patients presenting with contraindications. These might include general contraindications against non-invasive techniques, such as aforementioned lack of airway-protective reflexes, but also such specific for tight masks, such as anatomical abnormities of the face[8,9].

High-flow Nasal Oxygen

High-flow nasal oxygen ($HFNO_2$) therapy is usually applied via a wide-bore nasal cannula. It provides up to 60L/min of a heated and humified gas mixtures (at an adjustable mix medical of oxygen and room air). This therapy is much less invasive for the patient, and thus often better tolerated.

$HFNO_2$ has been increasingly used in the last years for hypoxic respiratory failure (i.e. type I failure), and numerous studies have shown its efficiency in this indication both at the intensive care unit and at the emergency

department[10-15]. A recent systematic review and meta-analysis has concluded in improved patient comfort and reduced dyspnea scores[16].

Despite this good evidence for $HFNO_2$ in hypoxic respiratory failure, it has only reluctantly been used for hypercapnic respiratory failure. This might in a large part be explained by the fact that patients with chronic hypercapnia are known to diminish their their respiratory drive when exposed to hyperoxia[17]. However, evidence has begun to change on this indication in recent time. $HFNO_2$ has been shown to generate PEEP, despite not being a closed system[18], and to improve CO_2 clearance by flushing anatomical dead space[19]. It might also help to reduce inspiratory resistance and facilitate secretion clearance from humidified gas[20]. A study on COPD patients showed an increase in breathing pressure amplitude and mean pressure, as well as tidal volume, with a trend towards reduction of pCO2[21].

Based on these findings, the use of $HFNO_2$ has increased in clinical practice, and a number of case reports and -series indicate successful use[22-24]. Fraser et al. successfully investigated the use of $HFNO_2$ in patients with chronic COPD[25], and Jeong et al. retrospectively analyzed changes in arterial blood gases during use of $HFNO_2$ in the ED for both hypercapnic and non-hypercapnic patients, and found a significant reduction of pCO2[26].

There is, however, to date no randomized controlled trial investigating the effect of $HFNO_2$ in acute hypercapnic respiratory failure.

Objectives

To assess the efficacy and safety of $HFNO_2$ versus non-invasive CPAP ventilation support in acute hypercapnic respiratory failure.

Study

Setting

The study will be performed as a randomized controlled on-inferiority trial.

The study site is the Department of Emergency Medicine (ED) of the Vienna General Hospital, a leading academic research center for emergency medicine at a large, tertiary care hospital.

Around 90,000 patients are being treated at the department each year, approximately 150-200 of them suffering from hypercapnic respiratory failure, and requiring non-invasive ventilation support.

The department features its own ICU and intermediate-care unit, with 7 positions each, for a total of 14 positions capable of providing CPAP therapy. The Airvo II $HFNO_2$-device is also at regular use at the department.

Sponsoring

Sponsor of this study will be the Department of Emergency Medicine at the Medical University Vienna. There is no industry sponsoring or industrial financial support, but we will apply for financial support from research grants.

Registration and Regulation

This project is considered as a study investigating differences of two standard medical methods. This study will be submitted for review and approval to the ethical committee of the Medical University Vienna and the Vienna General Hospital. The office of the medical Director will be announced, and the study will be registered at http://www.controlled-trials.com/.

Population

Inclusion criteria

- Adult patients (e.g. at least 18 years old) treated at the Emergency Department
- Acute hypercapnic respiratory failure defined as a pCO_2>50mmHg and a pH<7.3 on admission

Exclusion criteria

- Patients being comatose on admission, with no intact airway, lac of airway-protective reflexes, or those who are not alert enough to follow commands
- Patients intubated by Emergency Medical Service
- Patients requiring intubation on admission
- Pregnant women

Outcome

Primary outcome

- Reduction of pCO_2 per hour

Secondary outcomes

Clinical and safety Parameters

- Frequency of therapy failure (switch to other therapy; intubation)
- Patient's perception of the therapy (10-point Likert-Scale from very uncomfortable to very comfortable)
- Adverse events

Efficacy Parameters:

- Time until pCO_2 reaches 50mmHg or less

Economic Parameters:

- Length of Stay at the Emergency Department

- Frequency of admission to ICU
- Frequency of admission to regular ward
- Length of Stay at the ICU
- Length of Stay at the Hospital
- Hospital readmission within 1 month

Methods

Randomisation

A random sequence will be generated by a person not involved in the enrolment of patients using standard software. Randomisation will be performed in variable blocks of 4 to 6, to yield an unpredictable allocation yet warranting balanced group sizes.

Sequentially numbered sealed opaque envelopes (SNOSE), containing allocation either to the intervention or the control group, will be pre-produced. The envelopes will be opened after consent immediately before the start of the intervention to allow for allocation concealment and reduce the risk of immediate post-random exclusion.

Intervention

Control consists of $HFNO_2$ using the Airvo II, Fisher & Paykel, New Zealand. A gas flow 60L/min and and a FiO_2 as clinically feasibile will be used. Therapy will be continued until a COHb-level of 50mmHg or less is reached, or therapy has to be aborted because of lack of tolerance by the patient or indication for intubation.

Control

Control consists of non-invasive CPAP ventilation support using a tight mask and standard respirator equipment of the Department of Emergency Medicine (Servo Ventilator 300, Siemens-Elema AB, Life Support Systems Division, Solina, Sweden). A positive airway pressure of 5cm H_2O and a FiO_2 as clinically feasibile will be used. Therapy will be continued until a COHb-level

of 50mmHg or less is reached, or therapy has to be aborted because of lack of tolerance by the patient or indication for intubation.

Based on treating physician's judgement, both intervention and control treatments might be aborted at any time, and any other therapy (simple Venturi-Mask, $HFNO_2$, non-invasive CPAP-ventilation support, intubation, extracorporal methods) might be initiated.

Measurement

Baseline characteristics and demographic variables will include age, sex, smoking status, prior diseases, especially any history of COPD or Asthma, and duration of treatment of those, medication, body size, pre-hospital treatment. pCO_2 levels will be measured using blood gas analysis at 0 – 15 – 30 – 45 – 60 – 90 – 120 (and every 30 minutes thereafter) minutes after the beginning of the therapy, and at the end of the therapy.

Patient's perception of the therapy will be assessed after the end of the therapy using a 10-point Likert-Scale from very uncomfortable to very comfortable.

In case of abortion of assigned therapy, we will follow a carry-on-latest principle, by calculating pCO_2 reduction per hour by dividing actual reduction of pCO_2 during assigned therapy by total treatment time (including follow-on therapy after abortion), to achieve a maximally conservative interpretation of therapy effect.

Statistics

Sample size

Sample size considerations are based on the primary outcome *pCO_2 reduction per hour*. Based on the published literature, we assume that the outcome in the control group is 4±3mmHg/hour[8]. Based on a clinically assumed non-inferiority of 2mmHg we would need 28 experimental subjects and 28 control subjects to be able to reject the null hypothesis, that the lower limit of a two-sided 90% confidence interval of the true difference between two groups is above the non-inferiority limit, at a power of 80%. Formally we will have to enrol 56 patients. To allow for potential loss to follow up, missing data, measurement issues, or other design factors we will increase actual sample size to 62.

In terms of feasibility, we expect approximately 150 to 200 eligible patients within one year, resulting in an expected study-duration of approximately 6 months.

Data Analysis

Baseline data and demographics will be tabulated for the intervention- and control-group to assess success of randomisation. Reduction of pCO_2 per hour will be calculated by dividing delta pCO_2 at start of therapy to end of therapy by duration of therapy in hours. In case of abortion of assigned therapy, we will follow a carry-on-latest principle, by calculating pCO_2 reduction per hour by dividing actual reduction of pCO_2 during assigned therapy by total treatment time. Reduction of pCO_2 per hour will be compared between individuals in the intervention and individuals in the control group. Primary analysis will follow the intention-to-treat principle. The unit of analysis will be single persons. We will calculate effects as differences with 95% confidence intervals. For hypothesis tests we will use the t-test or Mann-Whitney-U-test, as appropriate. In case of relevant clustering we will use regression-based approaches.

Categorical secondary outcomes will be analysed by calculating relative risks with exact standard error based 95% confidence intervals, and the Fisher's exact test will be used for comparison. Continuous secondary outcomes will be analyzed like the primary outcome. Length of stay data are expectedly lognormally distributed, therefore we plan to use log-transformed values for further calculations.

For data analysis we will use Stata 11. A two-sided p-value less 0.05 is generally considered statistically significant.

1.1.1.1 Privacy and Data safety

Directly and indirectly patient-related data will be stored physically and logically separated. In addition, only members of the study-group will have access to study data. Data will be stored on a secured computer of the department of emergency medicine and will be accessible only via restricted access for members of the study-group.

Literature

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