Official Tittle of the study:

Helmet CPAP versus High Flow Nasal Cannula Oxygen in Acute Cardiogenic Pulmonary Oedema: A Randomized Control Trial

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Objective:

To our knowledge, there has been no randomized trial comparing hCPAP with HFNC for management of patients with ACPE. The aim of this study was to compare the effectiveness of hCPAP with HFNC in emergency department in the management of ACPE, in terms of physiological outcomes, patient's comfort, intubation rate, and 28-days mortality.

Design:

This is a single center, randomized, controlled trial. The study was conducted from January 2018 to December 2018 in Emergency Department, Raja Permaisuri Bainun Hospital, Perak, Malaysia

Methods:

A randomization sequence was generated using Microsoft Excel Version 14.3.9 (Microsoft Corporation Redmond, WA) using permuted block randomization technique. Sequentially numbered, sealed and opaque envelopes were used to conceal randomized allocation. The person responsible for the randomization was not part of the clinical team. Participants were assigned to receive either helmet CPAP or HFNC in a 1:1 ratio.

Ethical approval from Medical Research and Ethics Committee of Malaysia Ministry of Health had been granted [NMRR-17-1839-36966 (IIR)]. Written informed consent was obtained from patient whenever possible or from the next of kin. An external data monitoring committee supervised data collection.

Participants

All patients diagnosed with ACPE was defined by sudden onset of dyspnea; presence of bilateral rales on auscultation, compatible physical examination (elevated jugular venous pressure, third heart sound on cardiac auscultation) with no medical history suggesting pulmonary aspiration or infection; or congestion found on chest radiograph [1].

Patients meeting all the following inclusion criteria (1) age $\geq$ 18 years (2) respiratory rate > 30 breath per minute and (3) pulse oximetry saturation (SpO_2)

< 90% with oxygen > 5 L per minute via reservoir facemask were included. Patient were excluded if they have one or more of the following criteria (1) altered mental status (GCS $\leq$ 14) (2) need for urgent intubation (3) hemodynamically unstable, or (4) pulmonary edema was believed to be non-cardiogenic causal.

Protocol

Upon arrival patients were supported on high flow non-rebreathing facemask with reservoir of oxygen 15 L/min. After enrolment they were randomized to receive either hCPAP or HFNC.

The helmet (CASTAR, Starmed, Italy) has gas inlet and outlet ports. The inlet port was connected to air and oxygen blender (Air Liquide, France). The outlet port was connected to a mechanical spring PEEP valve. Patient neck circumference was measured to ensure a tight but comfortable seal. The gas flow was set at minimum 40 L/min. PEEP was initially set at 5 cmH_2O with increments of 3-5 cmH_2O to achieve oxygen saturation of 94 -97%. Inspired oxygen fraction (FiO_2) was set at 0.6 and maintained throughout the treatment.

HFNC (Hamilton, C3S, INTELLiVENT, Switzerland) consists of an air-oxygen blender, which permits accurate adjustment of FiO_2 between 0.21 and 1.0 and delivery of gas flow up to 60 L/min through a heated humidifier (Hamilton H900, Switzerland). The gas mixture flows through a circuit at temperature of 37 °C and an absolute humidity of 44 mg/L to the patients. Large or medium nasal cannula were chosen according to patients' nostril size to limit air contamination. HFNC was first set at a gas flow of 50 L/min and a FiO_2 of 1.0, then was titrated to maintain SpO_2 of 94 – 97%.

In addition to the study intervention, patients received standard treatment consists of intravenous infusion of isosorbide dinitrate at initial rate of 1mg/hr, increased up to 10 mg/hr. Intravenous furosemide bolus of 40 mg or equal to patient pre-existing oral dosage were given if systolic blood pressure > 100 mmHg [1]. No sedative agent was given to patients. After the end of 60-

minute protocol, the chosen modality was continued at the discretion of the treating physician.

Early termination criteria included failure to tolerate NIV, worsening of respiratory failure (respiratory > 35 breaths/min, SpO_2 < 92%, PF ratio < 200, or signs of increased work of breathing such as use of accessory muscle), pulse rate > 120 beat/min or 30% increased above baseline, mean arterial pressure (MAP) increased > 30% above baseline prior intervention and deterioration of conscious level. If one or more of the criteria were encountered, intervention was escalated to intubation and mechanical ventilation. These patients were excluded from the final data analyses. The decision was made by the managing physician without the involvement of the researcher team.

Respiratory rate, heart rate, systolic and diastolic blood pressure, peripheral capillary oxygen saturation, arterial blood gaseous were obtained before beginning of the ventilation procedure and at 1 hour of ventilation. At these points, HACOR score, dyspnea scale using Visual Analogue Scale (VAS) and Likert scale were also obtained.

Dyspnea score measured using an unmarked 10cm VAS card that had mark with “I can breathe normally”, at one end correspond to patients’ normal baseline breathing which score “0” and on the other end “I can’t breathe at all”, which score “10” represent the worst difficulty perceived by patients [2].

HACOR is an acronym for heart rate, acidosis (pH), consciousness (GCS), oxygenation (PF ratio) and respiratory rate in which each parameter is an independent predictor for NIV failure [9]. HACOR score is out of 25 with differential weighting of each parameter. A HACOR score > 5 at 1 hour of NIV predicts > 80% risk of NIV failure and that early intubation guided by this score significantly improved mortality [3].

Study End Points

The primary outcome was a reduction in respiratory rate from prior to randomization to at 1 hour of treatment. The respiratory rate was measured directly by investigators, who auscultated and counted the breaths sound for

one full minute with a stethoscope. Secondary outcomes were improvements in (1) heart rate; (2) HACOR score; (3) arterial oxygenation PaO_2; (4) PF ratio; (5) dyspnea score; (6) intubation rate and (7) mortality rate 28-days.

Sample Size

Sample size calculation was obtained using G*Power Software version 3.1.9.4 by Franz Faul, University of Kiel, Germany (Copyright 1992-2019). Based on previous work, after 1 hour of intervention, there is a reduction in respiratory rate from 31 breaths/min (SD 3.7) to 22 breaths/min (SD 4.1) in HFNC group compared with a reduction of only 31 breaths/min (SD 3.9) to 25 (SD 3.6) breaths/min in control group [4]. We calculated sample size of 94 patients per group is necessary to get a trial power of 90%, a 1% type I error (2-sided tests) and 10% attrition rate.

Statistical Analysis Plan:

Data analyses were performed using SPSS (Ver.22 2013 IBM Corporation, USA). Data were analysed on the basis of priori-modified intention to treat. For continuous variables, results for each group are presented as means (SD) or median (interquartile range), according to the data distribution shape and type (nominal or ordinal). Dichotomous data are presented as number and percentage.

Primary outcome of respiratory rate difference and other normally distributed secondary outcomes were calculated using repeated measure ANOVA, a generalized mixed model with a compound-symmetry covariance matrix. Ordinal or skewed numerical data were analysed using Mann-Whitney U Test. Chi-square tests (or two-tailed Fisher exact tests when appropriate) were performed for categorical data. All tests were two-tailed with p-value of less than 0.05 were considered statistically significant.