Out of Hospital Non-invasive Ventilation in Adults with Acute Respiratory Failure

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A Capstone project submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements for the degree of Master of Physician Assistant Studies

University of Manitoba, Winnipeg

May 9, 2016

Abstract:

Introduction: Noninvasive ventilation (NIV) is commonly used in the inhospital treatment of acute respiratory failure. Studies have demonstrated that the use of NIV in acute respiratory failure reduces intubation rates, mortality as well as improves physiologic variables such as heart rate, respiratory rate, oxygen saturation and blood pressure.

Objective: This systematic review attempts to determine if the addition of prehospital NIV/CPAP to standard care reduces the rate of endotracheal intubation compared to standard care alone.

Methods: A systematic review was conducted in January 2016 using, PubMed, EMBASE and Scopus. Included studies were those that compared the addition of prehospital NIV/CPAP to standard care versus standard care alone in patients with acute respiratory failure. Randomized controlled trials, retrospective studies as well as before and after studies were included.

Results: Five studies met the inclusion criteria. Two randomized controlled trials, two retrospective studies and one before and after study. Three studies reported a decrease in the intubation rate, one specifically when CPAP was continued in the emergency department. Two studies reported an improvement in physiologic variables in the groups treated with CPAP. One study reported a shorter intensive care unit length of stay, and one study reported a decrease in mortality in the CPAP group.

Conclusion: Prehospital NIV/CPAP is an effective and safe treatment for patients with acute respiratory failure. The administration of prehospital NIV can reduce rates of endotracheal intubation and improve overall physiologic variables. However larger

randomized controlled trials are required to determine the implementation of prehospital CPAP in acute respiratory failure EMS protocols.

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Introduction

Acute respiratory failure is a critical clinical condition that can occur when the respiratory system fails to oxygenate (hypoxemic respiratory failure) and/or ventilate (hypercapnic respiratory failure), which is preceded by respiratory distress. Hypoxemic respiratory failure also referred to as Type I respiratory failure occurs when the partial pressure of oxygen in the blood (PaO_2) is below 60 mmHg with a normal partial pressure of carbon dioxide in the blood ($PaCO_2$) (1). Hypoxemic respiratory failure occurs when certain areas of the lung are unable to perform gas exchange, while others remain unaffected, therefore maintaining normal partial pressure of carbon dioxide (1,2). Some of the most common causes of hypoxemic respiratory failure are acute cardiogenic pulmonary edema (ACPE), pneumonia, pneumothorax and pulmonary embolism (1,2). The second form of respiratory failure, hypercapnic respiratory failure is also referred to as Type II respiratory failure and is defined as a PaO_2 below 60mmHg accompanied with a $PaCO_2$ greater than 50 mmHg. Type II respiratory failure is a consequence of a reduction in total ventilation (1). The most common causes of hypercapnic respiratory failure are chronic obstructive pulmonary disease (COPD), asthma, drug overdose and neuromuscular disease (1,2). Respiratory failure can also be described as either acute or chronic. Acute respiratory failure can occur quickly and follows an insult to the lungs and the central nervous system. Chronic respiratory failure occurs over a long period of time and will coincide with metabolic disturbances found on arterial blood gas (2). A variety of signs and symptoms can be observed in patients in acute respiratory failure, such as: shortness of breath, use of accessory muscles, tachycardia, cyanosis, wheezing, fatigue, anxiety, and confusion (2).

The majority of patients in acute respiratory distress or failure will either present to the Emergency Department (ED) or call Emergency Medical Services. Emergency paramedics are trained to recognize the signs and symptoms of acute respiratory failure and within a short window of time stabilize the patient for transport to the nearest ED. Paramedics working on ground ambulances accomplish this task without the use of diagnostic imaging or laboratory testing.

Depending on the severity of the condition, patients presenting with acute respiratory failure may potentially require prehospital endotracheal intubation performed by paramedics. Although endotracheal intubation (ETT) is the gold standard for airway management, it is associated with an increase risk of ventilator acquired pneumonia (VAP) and local airway injury (3,4). Furthermore, prehospital ETT can be difficult to perform due to environment limitations, lack of experience and expertise in endotracheal intubation and advanced airways (5,6).

In order to avoid the potential complications of endotracheal intubation, non-invasive ventilation (NIV) has become standard of care in adult patients presenting with acute respiratory failure secondary to COPD, ACPE, in the emergency department (7). NIV is the delivery of ventilatory support, or positive pressure through facemask, nasal cannula or nasal mask. Non-invasive ventilation can be given in the form of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BPAP) (3,8). With CPAP, a continuous level of positive airway pressure is applied to the airway. This results in opening the airway, increasing lung volume in terms of functional residual capacity. Allowing gas exchange to occur due to greater surface area. Its most common uses are in obstructive sleep apnea, ACPE and obesity hypoventilation syndrome (9).

BPAP differs from CPAP in one simple way. BPAP delivers a pre-set inspiratory positive airway pressure as well as a pre-set expiratory positive airway pressure. This mimics the breathing cycle. The differences between these two pre-set values are what determine the tidal volume (9). The tidal volume is essential for improved removal of carbon dioxide, especially in type II respiratory failure.

The benefits of NIV have been seen in patients with acute or chronic respiratory failure, ACPE and chronic congestive heart failure with sleep related breathing disorders (3,8,9). Although there are many benefits to the use of NIV there are contraindications to its use as well. These contraindications are respiratory arrest, inability to generate adequate mask seal, uncontrolled emesis, severe upper GI bleeding, inability to clear secretions, airway obstruction, facial trauma, inability to protect airway, decreased level of consciousness, and patient decline (3,8,9). Thus, patients must be carefully screened and selected prior to using NIV.

NIV has been proven to be effective in COPD exacerbations, by decreasing the rate of endotracheal intubation, decreasing length of stay in hospital, as well as improving patient mortality (10–12). NIV has also shown a similar benefit in ACPE (10,11,13–15). Even more, Canadian practice guidelines recommend that NIV be the initial method of ventilatory support in patients presenting with ACPE or an acute exacerbation of COPD (16). In the past, out of hospital treatment of acute respiratory failure was limited to supplemental oxygen and pharmacotherapy (17–21). Today it is important to study if earlier application of NIV in the prehospital environment could lead to improved outcomes in patients with ARF.

Many EMS Acute Respiratory Failure protocols across the country include the application of NIV (22–24). However, there is conflicting information in regards to the effectiveness of the prehospital use of NIV/CPAP. This review attempts to determine whether the prehospital use of noninvasive ventilation/CPAP reduces the rate of endotracheal intubation (prehospital or in the ED).

Methods:

Literature Search

Published studies relevant to this review were identified by a search in the following databases: PubMed, EMBASE and Scopus. The following search terms were used: "respiratory failure", "respiratory insufficiency", "ventilatory failure", "prehospital", "out of hospital", "ems", "emergency medical services", "nippv", "non-invasive positive pressure ventilation", "bilevel positive airway pressure", "bipap", "bilevel", "cpap", "continuous positive airway pressure", "intubation rate", "endotracheal intubation", "intubation", and "mechanical ventilation".

Study Selection

Studies were selected based on the following inclusion criteria: studies consisting of controlled studies, which examined the addition of prehospital NIV to standard medical treatment in patients with acute respiratory failure of any cause versus standard medical treatment alone.

Following the initial search, studies that did not meet the inclusion criteria were excluded based on the flowing exclusion criteria:

1. Studies not involving NIV or CPAP

2. Not in a prehospital setting, ground EMS
3. Not acute respiratory failure of any cause
4. Not comparing CPAP/NIV + standard medical treatment to standard medical treatment alone
5. Not including intubation rate as an outcome measure
6. Patients under the age of 15
7. Abstract only
8. Studies not published in English

Studies were initially excluded if their title did not meet the inclusion criteria and duplicate studies found in multiple databases were also excluded. Once articles were selected based on their titles, the abstracts were then examined. If exclusion criteria could not be identified based on the abstract, the entire article was reviewed for exclusion criteria outlined above.

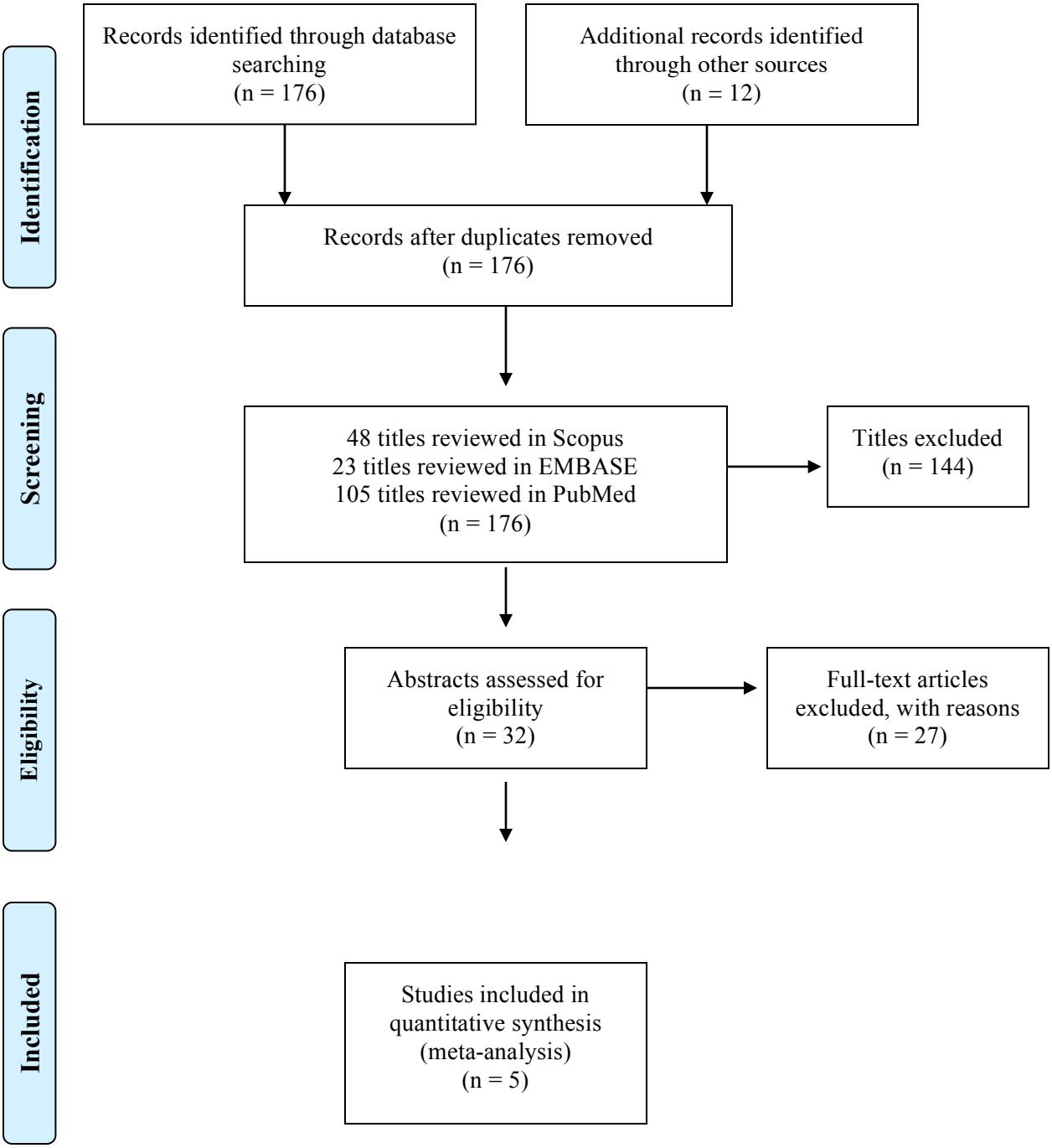
Process:

The database search using the search terms outlined above lead to the location of 105 studies searching PubMed, 48 studies in Scopus, and 23 studies in EMBASE. 12 additional articles were identified through the reference lists of published articles. 12 articles were duplicates and therefore were excluded. Of the studies identified in each of the databases, 144 titles were excluded because they did not meet the inclusion criteria. Of the remaining 32 articles, 5 studies that met the inclusion criteria as well as the outcome measures of interest were selected.

Outcomes:

The primary outcome of interest was the rate of endotracheal intubation, either in the prehospital setting or in the Emergency Department. Secondary outcome measures in the studies reviewed were hospital/intensive care unit length of stay (LOS), vital sign parameters, and mortality.

Figure 1: Prisma Study Flow Chart



Results:

Characteristics of Included Studies

Table 1 outlines the study characteristics and their main findings. The five studies selected were published between 2008 and 2015 and were conducted in 3 different countries one in Germany (20), two in Canada (18,19) and two in the United States (17,21). Of the five studies selected, two were randomized controlled trials comparing the efficacy of the addition of CPAP/BPAP to standard medical treatment (SMT) versus SMT alone in the prehospital environment. The three remaining studies were retrospective controlled studies evaluating the same.

Four studies (17–19,21) evaluated the effectiveness of CPAP while one study (20) evaluated the use of CPAP and BPAP. Two of the included studies were conducted in Canada (Ontario and Nova Scotia) (18,19), two were conducted in the United States (New Jersey and California) (17,21) and one study was took place in Germany (20). The studies conducted in North America compared the use of the addition of CPAP to SMT in acute respiratory failure to the use of SMT alone. SMT in one study was limited to oxygen therapy via nasal prongs, non-rebreathe mask or nebulizer therapy as well as treatment with an intravenous diuretic (furosemide). SMT in the three other studies consisted of use of bronchodilators, nitrates, diuretics as well as oxygen therapy. Roessler et al. (2011) compared the use of BPAP and SMT with SMT alone consisting of bronchodilators and inhaled corticosteroids for patients presenting with presumed COPD, and for patients presenting with presumed ACPE they treated with diuretics (furosemide) in combination with a α_1-adrenoceptor antagonist (urapidil).

Table 1: Study Characteristics						
Author, year, country	**Design (n)**	**Population**	**Intervention**	**Comparator**	**Primary outcomes** ***Secondary outcomes***	**Primary results** ***(SMT vs. SMT+NIV)*** ***Secondary results***
Roessler, M. S. et al. (2012) Germany	RCT (n = 51)	Presumed ACPE, COPD, pneumonia with signs of hypoxia (SpO_2<90% RA),or ventilator failure (SpO_2 <90% + RR >20 breaths/min)	SMT + CPAP/BPAP (n = 24) Provider: physician	SMT: O_2, reproterol+/- dexamethasone (COPD) furosemide+/- urapidil (ACPE)(n = 25)	Efficiency of treatment *ICU- LOS (days),* *H-LOS (days),* *28 day survival,* *ETT*	80% vs. 100% (p=0.05) *3.7 vs. 1.3 (p=0.03)* *17.4 vs. 13.9 (p=0.5)* *92% vs. 96% (p=1)* *24% vs. 4% (p=0.66)*
Dib, J et al (2012) Unites States	Retrospective review of hospital charts, controlled (n = 387)	Presumed CHF RR>25 breaths/min, intact mental status, SOB, bilateral rales, history of CHF	SMT + CPAP (n = 149) Provider: paramedic	SMT: O_2, nitrates, furosemide, morphine (n = 238)	Transport time *Physiologic variables* *ETT*	30 min vs. 31 min (p>0.01) *Overall improvement (p's<0.01)* *5.46% vs. 2.6% (p<0.01)*
Thompson, J et al (2008) Canada	RCT (n = 71)	ARF of any cause, accessory muscle use, RR>25 breaths/min, hypoxia	SMT + CPAP (n = 35) Provider: paramedic	SMT: O_2 , nitrates, diuretics, morphine, bronchodilators (n = 34)	ETT I*CU-LOS (days),* *H-LOS (days),* *Mortality*	50%v. 20% (adjusted OR 0.16; 95%CI 0.04-0.7) *No difference 6.5 v.3* *No difference 7 v. 9* *35.3% v. 14.3% (OR 0.3; 95% CI 0.09-0.99*)

Table 1: Study Characteristics cont'd

Author, year, country	**Design (n)**	**Population**	**Intervention**	**Comparator**	**Primary outcomes** ***Secondary outcomes***	**Primary results** ***(SMT vs. SMT+NIV)*** ***Secondary results***
Willmore, A et al 2015 Canada	Before and after, observational (n = 112**)	Presumed ACPE or COPD 2 of the following: SpO_2<90%, RR≥24, accessory muscle use	SMT + CPAP (n = 66,31)* Provider: paramedic	SMT: O_2, bronchodilators, nitrates, ventilation with BVM (n = 46)•	Mortality: - Overall - Patients meeting CPAP criteria *ETT* *NIV in ED* *LOS (days)*	 14.9% v. 18.8% (p<0.0001) 10.9% v. 19.7% (p=0.21) *4.4% v.1.5% (p=0.47)* *21.7% vs. 31.8% (p=0.33)* *8.7 v. 6.8 (p=0.24)*
Aguilar, S et al 2013 United States	Retrospective, controlled (n = 410)	Presumed ACPE, COPD or asthma Minimum criteria: Accessory muscle use AND RR>25/min OR SpO_2<94% Additional criteria: 2 of RR >25, SpO_2≤ 85% or HR ≥ 100	SMT + CPAP (n = 175) Provider: paramedic	SMT : O_2, NP, non rebreathe or nebulizer therapy, furosemide (n = 235)	Physiologic variables ED (HR+RR) *Prehospital + ED ETT* *Overall outcome measures:* *H-LOS, ICU-admission, ICU-LOS, Mortality* *Secondary outcome measures:* *Continued vs non continued CPAP in ED: ETT, ICU LOS*	Favours non CPAP group p's <0.05 *No difference p's>0.05* *No difference p's >0.05* *ETT: 27.7% vs. 19.3% p=0.035* *ICU LOS 3 vs. 2 days (p=0.019)*

** 112 Dyspnea Patients Meeting CPAP Criteria in the Before and After Groups
*31 or 66 patients meeting criteria for CPAP in after group that received CPAP
•Patients in before group meeting CPAP criteria. ACPE: acute cardiogenic pulmonary edema, CHF: congestive heart failure COPD: chronic obstructive pulmonary disease, SpO_2: Oxygen saturation, RR: respiratory rate, HR: heart rate

Study Participants

The studies all evaluated acute respiratory failure or severe respiratory distress, however differed in etiology. One study was limited to patients with ACPE (21), one was limited to patients ACPE and COPD (19), another included patients with ACPE, COPD and pneumonia (20), the fourth included patients with ACPE, COPD, and asthma (17), and the last study evaluated ARF as a whole including patients with ACPE, COPD, asthma, and pneumonia (18).

A total of 1,031 adult patients (15 years of age or older) with ARF were enrolled in the five studies included in this review. Of the 1,031 patients, 390 received treatment with prehospital CPAP and 24 received treatment with prehospital BPAP. 578 patients were treated with standard medical therapy. The mean age of enrolled patients across the five included studies was 71.53 years and 51% were women. The five studies selected patients based on inclusion/exclusion criteria. All of the studies inclusion criteria evaluated respiratory rate (RR). Three studies inclusion criteria required a RR equal or above 25 (17,18,21), the study by Willmore et al. (2015) required a RR equal or above 24 in their inclusion criteria and the study by Roessler et al. (2012) required a RR equal or above 20 in their inclusion criteria. Other parameters included in the studies inclusion criteria was: oxygen saturation $\leq$ 90% in two studies (19,20) and $\leq$ 94% in one study (17). The studies by Thompson et al. (2008) and Willmore et al. (2015) also included the use of accessory muscles of breathing in their inclusion criteria. The study by Dib et al. (2012) evaluated the effect of prehospital CPAP for acute severe congestive heart failure, therefore the patients included in their study were required to have a history of congestive heart failure as well bilateral rales, heard on auscultation by paramedics.

Outcomes

Primary Outcome Measure: Endotracheal Intubation Rate (Prehospital or in Emergency Department)

All five studies evaluated the effect of prehospital non-invasive ventilation on endotracheal intubation rates either as their primary outcome measure or secondary outcome measure.

The first study evaluated the efficiency of non-invasive ventilation (NIV) in the prehospital setting (20). The treatment was deemed inefficient if five minutes after receiving SMT or NIV the oxygen saturation (SpO_2) was below 85% or had dropped to 85% or under and/or the respiratory rate (RR) was equal to or above 30 or had increased to equal or above 30. This study found that according to the failure rates described above, NIV was more effective than SMT, 100% versus 80% ($p = 0.05$). Included in the secondary outcome measures was the rate of invasive ventilation in hospital, this study found that 4% of patients in the NIV cohort required invasive ventilation as compared to 24% of patients in the SMT cohort ($p=0.66$).

The study conducted by Aguilar et al. (2013) examined the efficacy of adding prehospital CPAP to an urban EMS respiratory distress protocol when compared to standard medical treatment alone. Their primary outcome measure was the improvement of physiologic variables such as oxygen saturation (SpO_2), heart rate, and RR, however included in the secondary outcome measures was the rate of endotracheal intubation. The analysis of overall outcome measure demonstrated no difference in endotracheal intubation attempts between the post-CPAP intervention group and the SMT control

group (22.3% versus 17.7% (p = 0.151). However following stratification of patients who were continued on CPAP/ NIPPV in the Emergency Department in the post-implementation period, results regarding intubation in the ED favoured the cohort continuing CPAP/NIPPV in the Emergency Department, 19.3% versus 27.7% (p = 0.035).

The randomized controlled trial conducted by Thompson et al. (2008) evaluated the effect of out of hospital CPAP in patients in severe respiratory distress on intubation rates versus usual care. This study found that half of the patients receiving standard medical treatment alone required intubation (17 patients of 34) versus 20% of patients in the CPAP group (7 patients of 35), (unadjusted OR 0.25; 95% CI 0.09 to 0.73; adjusted OR 0.16; 95% CI 0.04 to 0.7). These results suggest that for every three patients presenting with severe respiratory distress and requiring out of hospital CPAP one intubation is prevented.

The fourth study examined was a retrospective study conducted by Willmore et al. (2015) who evaluated the effectiveness of prehospital CPAP in an urban setting. Their primary outcome measures were effectiveness and safety. The primary effectiveness outcome was defined as mortality; secondary outcomes evaluating the effectiveness of CPAP were prehospital and emergency department intubation rates, rates of NIV in the ED, disposition from the ED and length of stay (LOS). The study found that EMS intubation rates were low in both groups, with only one intubation in the "after" CPAP implementation group. Among the patients meeting CPAP criteria, there was no statistically significant in the rate of intubation in the Emergency Department (1.5% versus 4.4%; p = 0.47).

The last study evaluated the role of prehospital CPAP in patients in severe respiratory distress secondary to ACPE (21). The primary outcome they evaluated was the duration of prehospital paramedic treatment (i.e. transport time). The secondary outcome measures included endotracheal intubation rate and physiologic variables such as pulse, oxygen saturation, blood pressure, and RR. The results demonstrated a decrease in endotracheal intubation rate in the CPAP group versus the group receiving standard medical treatment (2.6% vs. 5.4%; $p < 0.01$).

Secondary Outcome Measures: Hospital Length of Stay (H-LOS), Intensive Care Unit Length of Stay (ICU-LOS), Vital Parameters, and Mortality

The study conducted by Roessler et al. (2012) included vital parameters, ICU-LOS, H-LOS in their secondary outcome measures. In comparison with the baseline vital parameters of each participant, respiratory rate, heart rate and blood pressure were lower ($p < 0.01$) at hospital admission in both the treatment group receiving NIV and the group receiving SMT. A rise in the oxygen saturation was observed in both groups, however a more rapid and stronger increase was observed in the NIV group ($p < 0.01$). In the NIV group the SpO_2 rose to 94.3 +/- 4.4% within five minutes of treatment versus 90.8% +/- 8.1% in the SMT group. At time of admission the SpO_2 rose further in the NIV group to 97.6% +/- 1.8% versus 96.6% +/- 3.7% in the SMT group. The length of stay in hospital did not differ between both groups (13.9 days NIV group vs. 17.4 days SMT group, $p = 0.50$) however the patients treated with SMT were more likely to be admitted to the ICU which led to longer treatment and stay (1.3 vs. 3.7 days $p = 0.03$).

As described above, the primary outcome measures of the second study by Aguilar et al. (2013) was to determine the effect of prehospital CPAP on physiologic variables such as SpO_2 %, heart rate, and respiratory rate. The secondary outcome measures included ICU-LOS, H-LOS and mortality. There were statistically significant differences in physiologic variables between the SMT group and the post-CPAP implementation group, favouring the SMT group (respiratory rate in ED 22 vs. 28; $p < 0.001$; heart rate in ED 102 vs 111; $p = 0.003$, no difference observed between both groups oxygen saturation, $p > 0.05$). No significant differences were found between the post-CPAP implementation group and SMT group in length of hospital stay (3.0 vs. 4.0 days; $p = 0.342$), length of stay in ICU (2.0 vs. 3.0 days; $p = 0.217$) and survival to discharge (90.9% vs. 87.7%; $p = 0.161$). With stratification by patients who were continued on CPAP in the ED, the patients who received CPAP in the ED had a shorter ICU-LOS (median 2 days versus 3.5 days, $p=0.019$)

The third study by Thompson et al. (2008) evaluated the rate of endotracheal intubation as the primary outcome measure. The secondary outcome measures consisted of ICU-LOS, H-LOS, and patient mortality. There was no statistical significant difference between both treatment groups in terms of ICU-LOS (SMT 3 vs. CPAP 6.5 days) and H-LOS (SMT 9 vs. CPAP 7 days). There were significant differences in mortality rates between both groups. A total of 12 out of 34 patients (35.3%) in the SMT group died versus 5 out of the 35 patients (14.3%) in the CPAP group (OR 0.3; 95% CI 0.09-0.99).

The fourth study conducted by Willmore et al. (2015) evaluated the effectiveness of prehospital CPAP in patients with acute respiratory distress secondary to ACPE, and COPD. The two main objectives of this study were to determine if CPAP was 1) an

effective treatment and 2) if it was safe. The primary outcome measure to determine if CPAP was effective was overall mortality. Hospital length of stay was also evaluated but considered a secondary outcome measure. Mortality in the emergency department among patients meeting the CPAP criteria was greater in the after CPAP implementation group 7.6% versus 0% ($p < 0.05$). Overall mortality among the 321 dyspneic patients included in the before and after groups, was greater in the after group (18.8% vs. 14.9%, $p < 0.0001$). However there was no difference in mortality in the patients meeting CPAP criteria (after group 19.7% vs. before group 10.9%, $p = 0.21$). Hospital length of stay was longer in the after group 12.2 days vs. 6.6 days.

The fifth study evaluated physiologic parameters as a secondary outcome measure (21). They examined the effect of prehospital CPAP on oxygen saturation, blood pressure, pulse and respiratory rate. There was significant effect on all of the physiologic variables when comparing the CPAP group to the non-CPAP group; SpO_2 increased 9% versus 5% ($p < 0.01$). Systolic blood pressure decrease by 27.1 mmHg versus 19.9 mmHg ($p < 0.01$), diastolic blood pressure decreased by 14.4 mmHg versus 7.4 mmHg ($p < 0.01$), pulse decreased by 17.2 beats per minute versus 9.6 beats per minute ($p < 0.01$) and respiratory rate decreased 5.63 breaths per minute versus 4.09 breaths per minute ($p < 0.01$).

Limitations:

The five studies included in this review were all published in English. The search strategy limited the results to papers published only in English. By doing so relevant studies published in other languages may have been missed. By including only five studies in this review this may also have resulted in publication bias, due to the presence of other

relevant studies on this topic that were not included in the analysis. None of the studies included were completely blinded. The studies conducted by Thompson et al. (2008) and Roessler et al. (2012) were both randomized control trials, therefore reducing the risk of selection bias. However the three other studies included in the review were observational retrospective studies. The non-RCT studies may have an increased of selection bias due to the non-randomization of the study subjects, as well as the fact that the paramedics and patients were non-blinded to the use of CPAP. The retrospective studies by Dib et al. (2012), Aguilar et al. (2013) and Willmore et al. (2015) also demonstrate an increase risk of bias due to the retrospective nature of the data collection. All of the data was collected retrospectively and the identification of patients in acute respiratory failure (independent of the etiology) was made by reviewing EMS and hospital records based on patient history, treatment, outcomes, and in two cases reviewed by physicians (17,21).

Another difference noted between studies is where they took place. Four of the included studies were conducted in North America (two in the USA and two in Canada). The North American studies describe similarities between the healthcare systems with Emergency Medical Service teams staffed with paramedics. The study by Roessler et al. (2012) was conducted in Germany. The EMS system described in this study consisted of a two-tiered system. The first tier consists of an ambulance staffed with paramedics and the second tier consists of a vehicle staffed with an Emergency physician as well as a paramedic.

Germany's national regulations require that in the event of respiratory distress, both tiers are dispatched and expected to arrive on the scene in 15 minutes. With both teams of medical providers arriving to the scene at approximately the same time, the

treatment was administered either by an emergency physician or it was administered with the direction supervision of that said physician. In contrast with the North American studies one team of paramedics, consisting of advanced level paramedics and/or basic life support paramedics were dispatched to the scene and administered the treatment.

The paramedics involved in four of the included studies were required to participate in additional training on the use and application of NIV (17–19,21), the study by Roessler et al. (2012) did not implement additional training to the paramedics involved in the study due to the presence of an experienced physician that supervised the administration of NIV. This additional training varied among the studies, but included a lecture on CPAP followed by hands on training. All paramedics were educated on the indications of CPAP use as well as the proper use of the CPAP equipment. Despite the training underwent by paramedics in the study conducted by Willmore et al. (2015) out of the 66 patients that met CPAP criteria, only 31 patients received treatment with CPAP. The authors of the study indicated that there was no questionnaire or debriefing tool provided to the paramedics involved in the study in order to determine the cause of the discrepancy in the application of CPAP in patients who met CPAP criteria. They did however state that through discussion with the paramedics that the main barrier to CPAP application was the perception that patients had to be sick enough to require CPAP application. In all of the included studies, both treatment groups received SMT. The five studies compared the addition of NIV/CPAP to SMT to treatment with SMT alone in respiratory distress of various etiologies. In order to determine the severity of the respiratory distress and whether the patient's distress was appropriate for the study, each study had inclusion criteria that had to be met in order for the patient to be included in the

study. The inclusion criteria for each study included a variation of vital parameters and signs of respiratory distress such as blood oxygen saturation, respiratory rate, heart rate, use of respiratory accessory muscles, hypoxia and rales heard on auscultation. Despite including a blood oxygen saturation of under 90% as their inclusion criteria, the study conducted by Willmore et al. (2015) had the lowest rate of intubation across all five studies. These results may indicate that their study population was less sick than the study populations of the other included studies.

Lastly, all the included studies in this review were conducted in urban centres with short transport to hospital times. Therefore the generalizability of the prehospital use of NIV in acute respiratory failure cannot be made for rural centres and further research is required to determine the efficiency of prehospital NIV in a rural setting.

Discussion:

Five studies included in this review compared the use of prehospital non-invasive ventilation (CPAP/BPAP) with the use of SMT in patients in severe respiratory distress. The main outcome measure of this review was to determine the effect of pre-hospital NIV on the rate of endotracheal intubation. Two of the five studies showed a decrease rate in endotracheal intubation that was statistically significant (18,21). The study by Aguilar et al. (2013) showed no overall difference in endotracheal intubation rates between both treatment groups, however there was a significant difference in endotracheal intubation rates when the results were stratified by patients who were continued on CPAP/NIV in the emergency department versus those who were not continued on CPAP/NIV. The two remaining studies demonstrated a decrease in endotracheal intubation rates, however the values were not statistically significant. The

secondary outcome measures revealed improvement in physiologic variables in two studies, one study revealed improvement of physiologic variables favouring the patients receiving SMT. There were no differences among hospital length of stay in any of the included studies. The study by Roessler et al. (2012) reported an increase ICU-LOS in the patients receiving SMT and the study by Aguilar et al. (2013) reported a shorter ICU-LOS in patients continued on CPAP in the ED. The study by Thompson et al. (2008) was the only study that reported a difference in mortality. They reported an absolute reduction in mortality by 21% in patients who received CPAP versus usual care.

A variability of intubation rates was observed across the five studies, the rates ranging from 1.5% to 50%. These wide ranges can perhaps be explained due to the different causes of respiratory distress as well as the inclusion criteria of each study. The studies conducted by Thompson et al. (2008) and Roessler et al. (2012) included signs of hypoxia in their inclusion criteria, which may demonstrate that the patient population included in these studies were indeed more ill than the patients included in the other studies. As discussed above the studies were heterogeneous in terms of inclusion criteria this also may have had an effect on intubation rates. The use of inhospital non-invasive ventilation in ACPE has been widely researched. Multiple meta-analysis and systematic reviews have demonstrated that treatment with NIV reduces the need for endotracheal intubation as well as improves physiologic parameters (13,14,25). However, there is conflicting information on the effect of NIV on mortality. Systematic reviews have demonstrated that the use of NIV reduces the rate of mortality in patients with ACPE (13,14,25). However the meta-analysis conducted by Weng et al. 2010 that reviewed randomized controlled trials comparing the use of CPAP and BPAP with standard

medical therapy or each other in patients with ACPE found that the use of CPAP compared with SMT reduced mortality. Furthermore, the use of BPAP in comparison with standard medical therapy did not reduce mortality rates (15). Similar results have been observed with the use of NIV in patients suffering from an acute exacerbation of COPD. A systematic review conducted by Ram et al 2010, included 14 RCTs with a total of 758 patients. They determined that administration of non-invasive positive pressure ventilation resulted in a decrease in mortality, a decrease in the need for endotracheal intubation as well as an improvement in physiologic parameters (12). All of the studies included in this review, included patients in acute respiratory failure with a diagnosis of either ACPE, or chronic obstructive pulmonary disease. The study by Dib et al. (2012) was limited to patients with ACPE, the results coincide with the previous research on inhospital administration of NIV. However the studies that included acute respiratory failure secondary to various etiologies report conflicting data.

Asthma and/or pneumonia were included in the study populations of three of the included studies. Unlike ACPE and COPD, the use of NIV for the treatment of pneumonia as well as acute asthma attacks is controversial. A contraindication to the use of NIV is the inability to clear secretions; this commonly occurs in patients with a community-acquired pneumonia (CAP). However, if the patient is able to clear secretions as well as meet the requirements for NIV, many trials have demonstrated that the use of NIV in acute hypoxemic respiratory failure secondary to community acquired pneumonia (CAP) decreases the rate of intubation and mortality (26–28). One randomized study determined that patients with CAP with an underlying diagnosis COPD treated with NIV

had increased 2-month survival when compared to patients receiving standard therapy (26).

There is a lack of data surrounding the use of noninvasive ventilation to treat acute asthma, however it is commonly used in the treatment of asthma exacerbations. A Cochrane review published in 2012, examined 5 studies with a total of 206 patients. Two studies evaluated the rate of endotracheal intubation, in which two patients out of 45 in the NPPV group required intubation and zero patients of 41 of the control group required intubation. There were no deaths recorded in any of the included studies (29). Based on their findings, there is a lack of data in regards to the effect of NIV in acute asthma attacks. Three of the included studies of this review included pneumonia and/or asthma in their etiology of acute respiratory failure, however stratification of results based on the etilogy of the ARF was not examined. Further research is needed to determine the effect of NIV on these diseases.

With the additional training required by paramedics, as well as the cost of equipment, the National Institute for Health Research published a systematic review and cost effectiveness evaluation on the prehospital use of NIV for acute respiratory failure. The review determined that CPAP decreased mortality (OR 0.41, 95%CI 0.20-0.77) as well as decreased intubation rate (OR 0.32, 95% CI 0.17-0.62) versus standard care. They also stated although CPAP was more effective it was also more costly when compared to standard therapy. They reported that the cost-effectiveness of CPAP is uncertain and therefore further evidence on the feasibility, cost-effectiveness, and clinical effectiveness are required (30).

With over 600,000 Canadians suffering from heart failure and with 50,000 new cases of heart failure diagnosed every year, more and more Canadians with heart failure cost the health care system more than 2.8 billion dollars per year. This includes, emergency room visits, hospital admissions, medications and much more (31). Furthermore, statistics on hospital admissions collected by the Canadian Institute for Health Information (CIHI), reports that COPD is the most common cause of hospital admissions amongst all major chronic illnesses (32). The average length of stay for a patient suffering from a COPD exacerbation is of eight days, tallying to approximately $10,000 per stay (33). The study published by Mittmann et al. in 2008 estimated that COPD hospital admissions cost the healthcare system 1.5 billion dollars per year. With these drastic numbers, if treatment with prehospital non-invasive ventilation can either prevent hospital admissions or reduce hospital length of stay by reducing endotracheal intubation rates, it should be administered as early as possible, therefore be implemented in EMS respiratory distress protocols.

Conclusion

Prehospital NIV is a safe and efficient treatment for acute respiratory failure. The use of prehospital NIV has shown to reduce endotracheal intubation rates, especially when NIV is continued in the emergency department. However, these results may not be generalizable due to differences between health care systems, EMS staffing and inclusion criteria of each study. With the cost of paramedic training, equipment cost, as well as equipment upkeep (gear damage from frequent transports), further studies are required to determine the cost-effectiveness of prehospital CPAP. Limitations of this review are the heterogeneity of the included studies in terms of the inclusion criteria, the differing EMS

systems, the etiology of the respiratory distress, the inclusion of a small number of studies, few RCTs, the RCTs included had small sample sizes. Larger randomized controlled trials on the efficacy of prehospital NIV versus standard care are required in order to recommend the implementation of prehospital NIV in acute respiratory failure.

Acknowledgements

The author would like to thank Dr. Erin Weldon, for her mentorship, help and guidance throughout the completion of this project as well as Dr. Deni Pirnat, Dana Conrad, Dianna Wachtel and Ian Jones of the MPAS faculty for their continued guidance throughout the program.

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