HELMET NON-INVASIVE VENTILATION IN ACUTE RESPIRATORY FAILURE: A SYSTEMATIC REVIEW, CASE SERIES AND PILOT FEASIBILITY TRIAL

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TITLE: Helmet Non-Invasive Ventilation in Acute Respiratory Failure: A Systematic Review, Case Series and pilot feasibility trial

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This thesis consisted of three related studies presented as three separate manuscripts (one published in a peer-reviewed journal, one submitted for publication to a peer reviewed journal and one ongoing). The overarching theme of this thesis was to assess helmet non-invasive ventilation (NIV) as a new modality of NIV for the treatment of acute respiratory failure in the intensive care (ICU) setting.

Our first manuscript is a published systematic review and meta-analysis that compared helmet NIV to facemask NIV and high flow nasal cannula (HFNC) in adult patients with acute respiratory failure. We performed an extensive search and included 16 randomized control trials (RCTs) and 8 observational studies, the results of which we pooled separately. We assessed certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Pooled data from RCTs suggested that helmet NIV may reduce mortality and intubation when compared to facemask NIV, albeit based on low certainty evidence. Data from observational studies supported this finding but were of even lower certainty.

Given the above findings, we concluded that a large randomized control trial (RCT) that compared helmet to facemask NIV for patients with acute respiratory failure (ARF) is needed. Since helmet NIV is a new technology, before embarking on this large trial, we recognized that it was necessary to establish familiarity with the device and conduct a pilot feasibility trial. Manuscript # 2 was a 16 patient case series that characterized introduction of the helmet NIV at 2 centres (one in Canada and one in the United States). All patients who were admitted with ARF over a 7 month time period and for whom the clinical team determined that helmet NIV may be beneficial were enrolled in the trial. The most common reason for helmet NIV usage was pneumonia, especially due to COVID-19. Most patients tolerated helmet NIV and no adverse events were recorded with the device. This case series has been submitted to a peer reviewed journal for review.

After the case series had concluded and staff were introduced to helmet NIV, we initiated an ongoing single centre pilot feasibility RCT comparing helmet to facemask NIV in patients with ARF (manuscript #3). This pragmatic, unblinded, concealed allocation, parallel-group trial is currently being implementedat the Juravinski Hospital and will include 50 patients. The pilot trial will examine feasibility outcomes includingrecruitment rate and protocol adherence rate. While still ongoing, current feasibility goals have been met, although we noted a high crossover rate and decreased enrollment during the peak of the most recent COVID wave. These considerations have necessitated modifications to the protocol including planned enrollment of a second site, increased site education and new incentives for healthcare workers to enroll patients in the study. Funding for this trial was provided by securing 2 peer reviewed grants totalling $75,000.

Together, all 3 manuscripts represent an ongoing, cohesive research program aimed at assessing implementation and adoption of new technology in the ICU. Further projects examining the cost-effectiveness of this new technology, qualitative patients and healthcare worker experiences, as well as the aforementioned large multicentre RCT are planned moving forward.

ACKNOWLEDGMENTS

I would like to thank my thesis committee for their support and counsel without which this project would not have been successful. Karen Burns who initially provided the idea for a project based on the helmet NIV, before it was even approved in Canada has been an amazing mentor to me since I was a third year resident. From always setting time aside for me when I requested it, to providing valuable feedback and criticism, her guidance has been essential throughout this process. Deborah Cook, who has been an inspiration and a role model in how to be an amazing scientist and an amazing clinician at the same time. Despite everything else that she has going on, she has always been incredibly attentive to my questions and concerns and I've always appreciated her advocacy on my behalf. Finally, Bram Rochwerg, my lead supervisor who I've felt has always looked out for me since I started as an ICU fellow at McMaster. Whether it be inviting me to amazing collaborations or finding new opportunities for me to share my research or advance my career, I've really appreciated the fact that he's always looked out for my best interests. Moreover, he's always available for a chat whenever/wherever I need and that might be the most valuable thing a supervisor can provide. I would also like to thank other research supporters and mentors who helped me out during this thesis, but were not part of the committee, including Josh Piticaru, Tommaso Mauri and Tim Karachi.

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DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is submitted in partial fulfillment of the requirements for the Master of Science program in Health Research Methodology. The work takes the form of a sandwich thesis, consisting of three separate, but related manuscripts.

Dr. Dipayan Chaudhuri is the first author of all three manuscripts. He developed the protocol for all three studies, under the mentorship of his committee. For the systematic review and meta-analysis, he was involved in title and abstract review, case report form generation, data abstraction, analysis and GRADE application. For the case series, he was again involved in case report form generation, data collection and analysis. Finally for the pilot trial, he was responsible for the generally day to day operation of the study, case report form generation and data analysis. He also wrote the first draft of each manuscript before soliciting input and revisions from the committee.

INTRODUCTION

Invasive mechanical ventilation is associated with harm and should be avoided, if possible

Acute respiratory failure (ARF) is present in more than 50% of all ICU patients[1]. Endotracheal intubation and invasive mechanical ventilation (IMV) are the primary forms of respiratory support for patients with ARF in the ICU. However, endotracheal intubation carries significant risk, with approximately 25% of all adverse events in the ICU occurring in the peri-intubation setting[2]. Furthermore, IMV exposes patients to increased risks of ventilator-associated pneumonia (VAP), gastrointestinal bleeding, and ICU-acquired neuromuscular weakness, all of which increase morbidity and mortality [3].

Non-invasive ventilation may help to avoid intubation and the complications of IMV

Non-invasive ventilation (NIV) has been increasingly used as an alternative to endotracheal intubation and IMV[4], especially in patients with less severe respiratory compromise. NIV has been shown to reduce morbidity and mortality when compared to standard oxygen therapy, and in some cases IMV[4], especially in certain patient populations. To this end, the most recent ERS/ATS guideline strongly recommends NIV use for patients who have acute respiratory failure due to chronic obstructive pulmonary disease (COPD) exacerbations or cardiogenic pulmonary edema and conditionally recommends its use in patients with ARF due to a variety of etiologies including trauma, post-operative respiratory failure and for patients who are immunocompromised [5].

Typically, NIV is delivered through a face mask interface, however, at higher pressure levels, the face mask can be difficult to tolerate and may cause significant air leaks, thus impairing oxygenation and ventilation[6]. Furthermore, some patients may experience claustrophobia and patients who are delirious may have difficulty tolerating the face mask[7].

The helmet interface has potential advantages over the facemask interface

The helmet interface is a new modality that can be used to deliver NIV to patients with respiratory failure. A transparent hood is placed over the entire head of the patient with a seal at the neck using a soft collar. The helmet reduces air leak and improves tolerability due to lack of contact with the patient's face and better seal integrity at the neck[8]. The ability to provide a better seal and not obscure the face also provides the helmet NIV with a few unique applications. For example for pandemic-related illnesses such as coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS), the helmet may be a safer route to provide non-invasive respiratory support. Simulation studies have demonstrated the superiority of the helmet interface when compared to other non-invasive modes of respiratory support in the context of reduced exhaled viral dispersion[9, 10]. However, this phenomenon has not been sufficiently examined in actual patients. For patients with ARF following extubation, the helmet interface can be concurrently applied with high flow nasal cannula (HFNC) and other nasal respiratory support devices. Moreover, the helmet interface allows patients to speak, eat and drink, none of which are not possible with the face mask interface.

Low certainty data suggest that the helmet may be superior to the facemask interface

Early studies suggest several benefits associated with helmet NIV including better tolerance, lower intubation rates, lower mortality, fewer ventilator free days and ICU length of stay[6, 11, 12]. A recent network meta-analysis comparing all non-invasive oxygenations strategies in patients with acute hypoxemic respiratory failure showed lower mortality with helmet NIV compared to conventional oxygen therapy[13]. The helmet interface itself has been further refined to enhance patient comfort and reduce air leaks. Moreover, although the helmet interface purchase price is greater than the traditional facemask mask ($200 vs $35), a previous costing study led by Dr. Chaudhuri (the author of this thesis)[6] suggested that by reducing intubation and length of stay, the helmet interface may actually be cost saving[14]. A more comprehensive economic analysis incorporating the current best evidence is needed to validate these findings.

Summary

Although the helmet NIV interface has been more commonly used in Europe than elsewhere, especially during the COVID pandemic [15] with promising initial results, a lack of large-scale, well designed and adequately powered studies has limited its adoption worldwide. With regulatory approval now across North America, if these preliminary results are confirmed, it is possible that helmet NIV could improve clinical management of acute respiratory failure and decrease costs across broad populations. While other investigators are currently studying applications of the helmet NIV, to our knowledge, there have been no large multicentre RCTs comparing helmet NIV to face mask NIV in patients who present with both hypoxic and hypercapnic respiratory failure. Without further centre specific experience and direct RCT evidence, the utility of helmet NIV is yet to be definitively established.

Manuscript # 1 - Helmet Non-Invasive Ventilation compared to Facemask Non-Invasive Ventilation and High Flow Nasal Cannula in Acute Respiratory Failure: A systematic review and meta-analysis.

Reference: Chaudhuri D, Jinah R, Burns KEA, et al (2021) Helmet non-invasive ventilation compared to facemask non-invasive ventilation and high flow nasal cannula in acute respiratory failure: a systematic review and meta-analysis. Eur Respir J 2101269. https://doi.org/10.1183/13993003.01269-2021

Helmet Non-Invasive Ventilation compared to Facemask Non-Invasive Ventilation and High Flow Nasal Cannula in Acute Respiratory Failure: A systematic review and meta-analysis

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Take Home Message

Helmet NIV may reduce mortality and intubation when compared to facemask NIV, however, large well designed RCTs are needed on this topic.

Conflict of Interest/Competing Interests

BF is supported by a Vanier Canada Graduate Scholarship. TM received personal fees from Drager, Fisher and Paykel, BBraun, all outside of the submitted work. All other authors have no conflicts of interest to report.

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Abstract

Background: Although small randomized controlled trials (RCTs) and observational studies have examined helmet non-invasive ventilation (NIV), uncertainty remains regarding its role. We conducted a systematic review and meta-analysis to examine the effect of helmet NIV compared to facemask NIV or high flow nasal cannula (HFNC) in acute respiratory failure.

Methods: We searched multiple databases to identify RCTs and observational studies reporting on at least one of mortality, intubation, ICU length of stay, NIV duration, complications, or comfort with NIV therapy. We assessed study risk of bias (ROB) using the Cochrane ROB tool for RCTs and the Ottawa-Newcastle scale for observational studies and rated certainty of pooled evidence using GRADE.

Results: We separately pooled data from 16 RCTs (n=949) and 8 observational studies (n=396). Compared to facemask NIV, based on low certainty evidence, helmet NIV may reduce mortality (relative risk (RR) 0.56, 95% confidence interval (CI) (0.33 to 0.95)), and intubation (RR 0.35, 95% CI (0.22 to 0.56)) in both hypoxic and hypercapnic respiratory failure but may have no effect on duration of NIV. There was an uncertain effect of helmet on ICU length of stay and development of pressure sores. Data from observational studies was consistent with the foregoing findings but of lower certainty. Based on low and very low certainty data, helmet NIV may reduce intubation compared to HFNC, but its effect on mortality is uncertain.

Conclusion: Compared to facemask NIV, helmet NIV may reduce mortality and intubation; however, the effect of helmet compared to HFNC remains uncertain.

The protocol for this systematic review is registered with PROSPERO (CRD42020222942)

The ERS/ATS clinical practice guideline strongly recommends NIV use for patients who have acute respiratory failure (ARF) due to cardiogenic pulmonary edema and exacerbations of COPD and conditionally recommends its use for patients with ARF due to other causes including trauma, post-operative respiratory failure and those with immunocompromise[5]. For patients with ARF, NIV is typically applied with an facemask interface[16]. However, at higher airway pressures, the facemask interface may be difficult to tolerate and associated with air leaks, thus impairing oxygenation and limiting the mean airway pressure that can be applied to maintain lung recruitment[6]. Additionally, patients may not tolerate the facemask mask due to claustrophobia or facial pressure ulceration[7].

The helmet interface is a relatively new interface for NIV delivery. A transparent hood is positioned over the patient's head with a seal at the neck using a soft collar. The helmet reduces air leak due to better seal integrity at the neck and improves tolerability because there is no direct contact with the patient's face[8]. In patients with potentially infectious respiratory illness such as Covid-19, the reduced air leak and attendant decrease in droplet dispersion is especially valuable[10]. Furthermore, when compared to the facemask interface or high flow nasal cannula (HFNC), the helmet reduces inspiratory effort, preserves lung volumes and allows for lower inspiratory support, possibly by mitigating air leak or allowing for more effective provision of positive end expiratory pressure (PEEP)[17–19]. A recent JAMA network meta-analysis comparing all non-invasive oxygenation strategies in patients with purely hypoxemic respiratory failure demonstrated that helmet NIV may lower mortality and the need for intubation compared to COT[13]. However, only a small number of randomized control trials (RCTs) were included in this review[6, 8, 11, 12, 20], and it did not evaluate other patient important outcomes such as complications, comfort or duration of NIV. Moreover, with a focus on only hypoxemic

respiratory failure, the effect of helmet NIV on the other forms of acute respiratory failure remained uncertain. The COVID-19 pandemic has increased helmet NIV use[15], however, uncertainty regarding the benefits and harms of helmet NIV in clinical practice remains. Given several recently published RCTs and observational studies evaluating helmet NIV, along with the shortfalls of the previous systematic review addressing the topic, we conducted a systematic review and meta-analysis to address the following research question: In adult patients with acute respiratory failure of all types, does use of helmet NIV reduce mortality, intubation rate, ICU length of stay, and the risk of complications compared to facemask NIV or HFNC?

Methods

We registered the protocol of this systematic review with PROSPERO (CRD42020222942) and report our findings using the PRISMA checklist (Supplementary Table 1).

Search Strategy and Selection Criteria

We performed a comprehensive search of following databases from inception until October 23, 2020: MEDLINE, EMBASE, Web of Science, The Cochrane Library, International HTA Database, EBSCO CINAHL Complete, LILACS, and WHO COVID-19 Global literature on coronavirus disease. The search was updated on March 31, 2021. We used keywords "noninvasive ventilation" or "oxygen inhalation therapy" or "oxygen therapy" or "respiratory insufficiency" or "respiratory insufficiency" or " adult respiratory distress syndrome" or "respiratory failure" or "acute respiratory failure" or "adult respiratory distress syndrome" or "continuous positive airway pressure" or "positive end expiratory pressure" AND "head

protective devices" or "helmet". We did not exclude trials based on language or quality. We searched the bibliographies of included articles and prior meta-analyses on the topic. We consulted experts in the field to identify unpublished studies. A copy of our search strategy is included in the Supplementary Materials.

Study Selection

Two reviewers (DW, RJ) screened citations independently and in duplicate in two stages; first examining the title and abstracts and then the full text of selected citations. We captured reasons for study exclusion after reviewing the full texts of identified trials. A third reviewer (BR) adjudicated disagreements.

We included parallel group and crossover RCTs and observational studies that had an intervention and comparator cohort. We included studies that compared helmet NIV to NIV through another interface or HFNC in adult patients with ARF of any etiology. Included studies had to report at least one of the following outcomes of interest: mortality, intubation rate, duration of mechanical ventilation, ICU length of stay, hospital length of stay, patient comfort, modality tolerance and NIV related adverse events. We excluded observational studies without comparative analysis as well as case studies and case reports.

Data Extraction and Quality Assessment

Two independent reviewers (DC and RJ) working in pairs abstracted data in duplicate using a standardized data abstraction form. We collected data on trial characteristics, demographic data, interventional and control details, and outcomes. A third reviewer (BR) adjudicated disagreements where needed.

We assessed risk of bias (ROB) in duplicate using the modified Cochrane risk of bias tool 2 for RCTs[21]. We assessed each RCT using following domains: randomization sequence generation, allocation concealment, blinding, incomplete data, selective reporting, and other bias. For each domain, we rated ROB to be "low", "high", or "some concerns". The overall ROB for each trial was the highest risk attributed to any domain except for blinding (of the caregiver and patient specifically), as blinding is infeasible even with sham devices for these trials. For observational studies, we used the Newcastle-Ottawa scale[22] and assessed each cohort or case control study using the following domains: selection, comparability, exposure/outcome. For each domain, we rated ROB by a star system, whereby the greater number of stars, the lower the ROB. We assessed overall certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework[23]. To assess for publication bias, we also created funnel plots for the outcomes of mortality and intubation.

Data Analysis

We pooled RCTs and observational studies separately. In keeping with GRADE methodology, when presenting pooled data from both RCTs and observational data, we focused on the results with the higher certainty. We used the DerSimonnian-Laird random effects model with inverse-variance weighting to generate pooled treatment effects across studies. We assessed heterogeneity between trials using a combination of the Chi^2 test, the I^2 statistic, and visual inspection of the forest plots [24]. We present results of dichotomous outcomes using relative risk (RR) and continuous outcomes as mean difference (MD) with 95% confidence intervals

(CIs). We also tabulated absolute differences with 95% CIs. We performed all statistical analysis using RevMan 5.3 (Cochrane Collaboration, Oxford) software.

We planned for five *a priori* subgroup analyses: (a) COPD/hypercapnic respiratory failure vs. non-COPD/hypercapnic respiratory failure patients (b) CHF/pulmonary edema patients vs. non CHF/pulmonary edema patients; (c) COVID-19 related ARF vs. non-COVID-19 related ARF patients; (d) immunocompromised patients vs. non-immunocompromised patients; and (e) high ROB studies vs. low ROB studies. *A priori,* we hypothesized that COPD patients, CHF patients, COVID-19 patients, immunocompromised patients and trials at high ROB would show greater benefit with helmet NIV therapy.

Results

Search Strategy and Study Characteristics

We reviewed 974 citations and included 16 RCTs (n=949)[6, 17, 25–38] and 8 observational studies (n= 396)[39–46] (Figure 1). We depict the characteristics of the included RCTs in Table 1 and the observational studies in Supplementary Table 4. RCTs included between 10 and 188 patients. Of the 16 included RCTs, 4 were crossover studies[17, 25, 27, 38] and 2 trials were only published in abstract form[31, 32]. Overall, 13 studies compared helmet NIV to facemask NIV where 3 trials compared helmet NIV to HFNC[17, 30, 32]. Three trials applied the helmet NIV in continuous positive airway pressure (CPAP) mode[28, 31, 32], and 13 trials applied bilevel helmet NIV[6, 17, 25–27, 29, 30, 33–38].

Six trials included patients with hypoxic respiratory failure, of which, one trial each focused on patients with ARDS[6], pulmonary edema[31], chest trauma[29], COVID-19[30] and two on mixed hypoxemic respiratory failure[17, 32]. Two trials examined patients with post-

extubation respiratory failure[27, 29], and the 8 remaining trials enrolled exclusively patients with hypercapnic respiratory failure/COPD[25, 26, 33–38]. In Supplementary Table 2a and 2c, we summarize the ROB for included RCTs. Six trials were adjudicated to have low or intermediate ROB[6, 17, 26, 29, 30, 34, 38], while the remainder were judged to be at high ROB.

Of the 8 observational studies, 4 were case control studies[40, 43, 45, 46] and 4 were cohort studies[39, 41, 42, 44]. Observational studies included between 20 and 99 patients. Three studies compared helmet NIV to HFNC[39, 42, 44] and 5 compared helmet NIV to facemask NIV. Four studies only used helmet CPAP as their intervention[39, 42, 44, 45], and 4 studies evaluated helmet NIV[40, 41, 43, 46]. Only one study examined patients with COPD[40], while the remaining 7 examined helmet NIV in patients with hypoxic respiratory failure. Of the studies evaluating hypoxic patient populations, 2 focused on patients with COVID-19 infection[39, 42], one evaluated patients with hematologic malignancies[45] and one assessed immunocompromised patients[46]. In Supplementary Table 2b, we summarize the ROB for the observational studies. Most studies were adjudicated to have low ROB except for 2 studies [39, 42] that did not match their comparison cohorts.

Outcomes

We summarized the GRADE certainties and pooled estimates for pooled outcomes in Supplementary Table 3.

Helmet NIV versus facemask NIV

Compared to facemask NIV, helmet NIV may reduce mortality (RR 0.56, 95% CI 0.33 to 0.95, low certainty, Figure 2) and intubation (RR 0.35, 95% CI 0.22 to 0.56, low certainty,

Figure 3). Observational data was consistent with these findings yet of lower certainty (e-Figure 1, e-Figure 2). Pooled data from RCTs suggested that helmet NIV has an uncertain effect on ICU LOS (MD 0.29 days less, 95% CI 2.31 days less to 1.74 days more, very low certainty evidence, Figure 4) and may have no effect on duration of NIV (MD 0.02 days less, 95% CI 0.15 days less to 0.11 days more, low certainty evidence, Figure 5). Observational data was again consistent with these findings but of lower certainty (e-Figure 4, e-Figure 5)

Helmet NIV has an uncertain effect on the risk of skin necrosis/pressure sores compared to facemask NIV (RR 0.60, 95% CI 0.19 to 1.37, ARR 8.1% lower, 95% CI 13.2% lower to 6.0% more, e-Figure 7, very low certainty). All other complications are summarized in Table 2 as they were too variably reported to allow for pooling. The most common complications were skin necrosis/pressure sores and gastric distension. Similarly, whether and how patient comfort scales were documented across trials did not allow for statistical synthesis so these are summarized in Table 2.

Helmet NIV versus HFNC

Compared to HFNC, low certainty evidence from RCTs suggest that helmet NIV may reduce intubation (RR 0.59, 95% CI 0.39 to 0.91, e-Figure 6) but has an uncertain effect on mortality (RR 0.72, 95% CI 0.40 to 1.28, very low certainty, Figure 7).

The pooled estimates from observational studies for both intubation (RR 0.69, 95% CI 0.27 to 1.73, e-Figure 5) and mortality (RR 0.77, 95% CI 0.16 to 3.75, e-Figure 6) are consistent in demonstrating uncertainty based on very low certainty evidence.

Subgroup and Sensitivity Analysis

For the outcome of intubation, we did not identify credible subgroup effects when comparing patients with hypercapnic respiratory failure to those with hypoxemic respiratory failure or when comparing high versus low or intermediate ROB trials in pooled analysis from either RCTs or observational studies (Figure 3, e-Figure 2, e-Figure 8). For the outcome of intubation, we also did not identify any credible subgroup effects when comparing high versus low or intermediate ROB trials (e-Figure 11). The remaining pre-planned subgroup analyses were not feasible due to lack of study level aggregate data (only one study included immunocompromised patients and two included patients with COVID-19).

Publication Bias

There was minimal publication bias for the comparison of helmet NIV to facemask NIV in terms of the outcomes of mortality and intubation (e-Figure 9, e-Figure 10). We did not perform funnel plots for the comparison of helmet NIV to HFNC due to the small number of included studies.

Discussion

Although the use of helmet NIV has steadily increased[15], the evidence supporting its use remains sparse. This systematic review and meta-analysis found that while available studies demonstrate that helmet NIV may be associated with lower intubation rates and mortality compared to facemask NIV, the certainty of these estimates remains low. The effect of helmet NIV on other clinically important outcomes including ICU stay, duration of NIV, and adverse events such as facial ulceration is uncertain. There was limited evidence to compare helmet NIV

with HFNC, and therefore we conclude that high quality randomized clinical trials are required to establish the net clinical benefits or harms of helmet NIV.

Compared to previous reviews, this systematic review and meta-analysis adds a number of new studies examining the role of helmet NIV in ARF[47] (12 new studies including 7 new RCTs[17, 28, 29, 31, 32, 37, 38]). Despite this, all included trials and observational studies were small. For example, the largest trial examining helmet NIV use was a 188 patient RCT that compared helmet NIV to HFNC[32]. Further, 2 included trials were only published in abstract form[31, 32] and 2 trials were of a crossover design and only examined short term outcomes[17, 38]. Although pooled data from this systematic review suggests that helmet NIV may be preferable to facemask NIV, the information size and event rates are low, contributing to important imprecision which limits the strength of inferences that can be made. Comparisons between the effects of helmet NIV versus HFNC are even more uncertain. Overall, this systematic review highlights the critical need for large, high quality RCTs comparing helmet NIV to both facemask NIV and HFNC, including patient-important outcomes and attention to possible adverse events.

Many questions regarding the net clinical benefits of helmet NIV remain. Although some trials and studies reported complications and patient-reported comfort with helmet NIV, we were unable to pool the majority of data on these endpoints due to infrequent and variable outcome reporting. Similarly, while current best trial evidence supports the use of facemask NIV in selected populations (patients with COPD, CHF, immunocompromised etc) [5], there is currently a relative dearth of evidence regarding the effects of helmet NIV in these patient populations.

Specifically in patients with hypercapnic respiratory failure, worsening hypercapnia, ventilator asynchrony and under assistance are common concerns[40, 48]. However, at least one study of helmet NIV has shown that adequate CO_2 clearance can be achieved with high gas flow rates[48] and a few others have shown that helmet NIV reduces inspiratory effort[17, 18] . Regardless, to address the aforementioned concerns, we compared patients with hypercapnic respiratory failure versus those with hypoxemic ARF in a pre-specified subgroup analysis. Although we did not find any credible subgroup effects based on available data, imprecision and low number of events underscore the need for further investigation.

The ability to provide a better seal compared to a facemask mask and not obscure a full facial view also provides the helmet with a few unique applications. For pandemic related illnesses, such as COVID-19, and severe acute respiratory syndrome (SARS), the helmet may be a safer route to provide non-invasive respiratory support. To this end, simulation studies have demonstrated benefits of the helmet interface when compared to other non-invasive modes of respiratory support in the context of exhaled viral dispersion[9, 10], although this aerosolization has not rigorously evaluated in patients. For patients with ARF who are post-extubation, HFNC can be concurrently applied with helmet NIV and other nasal respiratory support devices. Moreover, helmet NIV permits a full facial view, speaking and nasogastric (NG) feeding tubes, which is often not possible with facemask NIV. Whether these features translate into enhanced comfort, fewer cutaneous complications and other benefits remains unknown, as patient reported outcomes are lacking in this field. In addition, both CPAP and pressure support ventilation (PSV) modes have been used with helmet NIV for various causes of respiratory failure. While it is likely that certain modes will provide no benefit for certain conditions (CPAP for COPD), the

ideal mode for each cause of respiratory failure remains unknown. Finally, the cost-effectiveness of this new technology has not been examined. Although the helmet interface costs more than the traditional facemask interface, a previous costing study based on the RCT by Patel at al.[6] suggested that by reducing intubation and ICU length of stay, the helmet interface may actually be associated with cost saving; however, further clinical studies and a more comprehensive cost-effectiveness study is needed to confirm or refute these findings.

To our knowledge, this is the largest and most comprehensive systematic review and meta-analysis to assess helmet NIV compared to facemask NIV and HFNC. Strengths of this study include pre-registration, incorporation of a comprehensive search, assessment of GRADE certainty allowing for appropriate contextualization of results, and inclusion of 11 additional studies (including 8 RCTs) compared to a previously conducted review including 13 studies[47]. This review also has limitations. First, the total number of included patients and the number of events are small. Second, by including all studies that compared helmet NIV to either HFNC or facemask NIV, there was considerable clinical and methodological heterogeneity across trials, which nonetheless was not associated with statistical heterogeneity (inconsistency) for most outcomes. Acknowledging different design features informing this review, we analyzed studies that compared helmet NIV to facemask NIV and HFNC separately, and RCTs and observational studies separately. However, considerable clinical heterogeneity remained as we were unable to conduct most predefined subgroup analyses due to insufficient data. In particular, we were unable to separate studies that examined hypoxic respiratory failure by the underlying varying pathophysiological mechanisms. While this highlights the need for further study on how specific causes of acute respiratory failure respond to helmet NIV, the lack of inconsistency across our

outcomes of interest seems to suggest that the effect of helmet NIV is likely similar regardless of the cause of acute respiratory failure.

Conclusion

Compared to facemask NIV, helmet NIV may reduce mortality and intubation; however, the effect of helmet compared to HFNC remains uncertain. As application of this technology increases, large, well designed RCTs comparing helmet NIV to both facemask NIV and HFNC in patients with both hypoxemic and hypercapnic respiratory failure will be needed to help inform practice.

Table 1: Characteristics of Included Randomized Control Trials

Author	Year	Country	Type of Helmet	Settings for Helmet	Comparator	Settings Used Comparator	Total (n)	Select Inclusion Criteria	Outcomes Recorded
Adi et al.	2019	Malaysia	Helmet CPAP	Not Described	High Flow Nasal Canula	Not Described	188	Patients presenting to ED with cardiogenic pulmonary edema	Intubation Rate, Mortality, Patient Comfort
Adi and Salleh	2018	Malaysia	Helmet CPAP	Not Described	Facemask CPAP	Not Described	123	Patients presenting with acute respiratory failure	Patient Comfort
Ali et al.	2011	Turkey	Helmet NIV (CaStar)	Started at PEEP 5-7 with Pressure Support 10 cm H20 and adjusted until volumes of 6-8 ml/kg obtained. Fio2 titrated to keep SPO2>92%	Facemask NIV	Facemask NIV (set same way as helmet NIV)	30	Patients with COPDe	Intubation Rate, ICU Length of Stay, Complications, Patient Comfort
Antogali a et al.	2010	Italy	Helmet NIV (CaStar)	Inspiratory pressure was increased (+20%) and finely tuned according to the patient-ventilator synchrony until the respiratory rate was less than 30 bpm, accessory muscle activity disappeared, the patient was comfortable, and leakage was minimized.	Facemask NIV	Facemask NIV (set same way as helmet NIV)	40	Acute exacerbation of COPD was investigated in the semi recumbent position. Patients had to undergo 2 hours of Facemask NIV	Intubation Rate, ICU length of Stay, Duration of Mechanical Ventilation, Complications
Cakir Gurbuz et al.	2015	Turkey	Helmet NIV (CaStar)	Pressure Support was gradually increased by 2 cm H20 steps during the first hour of ventilation to observe adequate patient respiratory effort. The FiO2 rate was also increased gradually up to 50% by 5% steps to obtain at least 92% SpO2. Target 6–8 mL/kg tidal volume during the NIMV procedure.	Facemask NIV	Facemask NIV (set same way as helmet NIV)	48	COPD patients admitted to the respiratory intensive care unit	Intubation Rate, ICU Length of Stay, Duration of Mechanical Ventilation
Fasano et al.	2012	Italy	Helmet NIV (CaStar)	Not Described	Full Facemask NIV	Not Described	31	COPD patients admitted to a Respiratory Intensive Care Unit (RICU) for AHRF and supported with NIV	Intubation Rate
Grieco et al.	2020	Italy	Helmet NIV (DiMAR)	Pressure-support ventilation: initial pressure support was 8–10 cm H2O and then adjusted to permit a peak inspiratory flow of 100–150 L/min, up to a maximum of 20 cm H2O; PEEP was 10–12 cm H2O; pressurization time was set to the fastest possible	High Flow Nasal Canula	Not Described	15	Acute hypoxic respiratory failure defined by respiratory rate >25 breaths per minute, need for supplemental oxygen to maintain 90% SpO2, and evidence of pulmonary infiltrates on chest X-ray or computed tomography scan	Patient Comfort
Grieco et al.	2021	Italy	Helmet NIV (DiMAR + CaStar)	The ventilator was set in pressure support mode, with the following settings: initial pressure support between 10 and 12 cm H2O, eventually increased to ensure a peak inspiratory flow of 100 L/min; positive end-expiratory pressure between 10 and 12 cm H2O; and Fio2 titrated to obtain Spo2 between 92% and 98%	High Flow Nasal Canula	Flow was initially set at 60 L/min and eventually decreased in case of intolerance, Fio2 titrated to obtain peripheral oxygen saturation as measured by pulse oximetry (Spo2) between 92% and 98%, and humidification chamber was set at 37 °C or 34 °C according to the patient's comfor	109	COVID-19 patients with moderate to severe hypoxemic respiratory failure (PF ratio <200)	Intubation Rate, Mortality, ICU Length of stay, Complications, Patient Comfort
Liu et al.	2020	China	Helmet NIV	Not Described	Facemask NIV	Facemask NIV (set same way as helmet group)	26	COPD exacerbation with respiratory failure as defined by study protocol	Intubation, Mortality, Complications

Liu et al.	2020	China	Helmet NIV (CaStar)	Pressure was initially set at 8 cm H2O, positive end-expiratory pressure at 5 cm H2O, and FiO2 at 40%. According to the patient's clinical symptoms and their percutaneous blood oxygen saturation (SpO2), NIV supports were sequentially increased in 1–2-cm H2O increments. If respiratory distress and SpO2 did not improve, FiO2 was progressively increased in 5% increments to achieve an SpO2 > 92%.	Facemask NIV	Facemask NIV (set same way as helmet group)	59	Within 72 hours of chest trauma confirmed by imaging with moderate to severe hypoxemic respiratory failure as defined by the study protocol	Intubation Rate, Mortality, ICU Length of Stay, Duration of Mechanical Ventilation, Complications
Longhini et al.	2019	China	Helmet NIV (CaStar)	The same PEEP applied during the pressure support through a face mask trial and an upper airway pressure (Paw) limit to obtain the same overall Paw applied during the pressure support through a face mask trial. The trigger sensitivity was set at 0.5 V, whereas the default cycling was 70% of the peak electrical activity of the diaphragm (EAdi), as fixed by the company. FIO2 was set to maintain peripheral (SpO2) between 90% and 94%.	Full Facemask NIV	Full face mask NIV (The ventilator was set as previously clinically indicated by the attending physician. Inspiratory pressure support was 8 cm H2O to obtain a tidal volume of 6 – 8 mL/kg of ideal body weight, with the fastest rate of pressurization and cycling that was between 25 and 50% of peak inspiratory flow.)	10	History of COPD admitted to ICU for exacerbation and acute respiratory failure as defined by the study protocol	Patient Comfort
Navalesi et al.	2007	Italy	Helmet NIV (CaStar)	Inspiratory assistance of 12 cmH2O, delivered using the highest pressurization rate, above a positive end expiratory pressure (PEEP) of 5 cmH2O, was used for all patients. This was preceded by periods of spontaneous unassisted breathing through a mouthpiece with the nostrils closed by a nose-clip and the ventilator set in continuous positive airway pressure (CPAP) mode at 5 cmH2O. FiO2 was set to obtain an oxygen saturation ≥ 93% and ≤ 96% during the first trial of spontaneous unassisted breathing and never changed throughout the study period. All the trials lasted 30 min.	Facemask NIV	Facemask NIV (set same way as helmet group)	10	History of COPD, chronic hypercapnic respiratory failure, long-term NIV via nasal mask as accordance to study protocol for at least 6 months with recent exacerbation	Patient Comfort
Patel et al.	2016	USA	Helmet NIV SeaLong	PEEP was increased in increments of 2 to 3 cm H2O to improve oxygen saturation to more than 90% at an inspired oxygen fraction (FIO2) of 60% or less, if possible. Inspiratory pressure was increased in increments of 2 to 3 cm H2O to obtain a respiratory rate of less than 25/min and disappearance of accessory muscle activity.	Facemask NIV	Facemask NIV (set same way as helmet group)	83	ARDS patients as defined by the Berlin criteria requiring facemask NIV	Intubation Rate, Mortality, ICU length of Stay, Hospital Length of Stay, Complications
Pisani et al.	2015	Italy	Helmet NIV (CaStar)	Set a positive end-expiratory pressure (PEEP) of >5 cmH2O and an inspiratory pressure support of ⩾16 cmH2O, keeping a flow rate >30 L·min-1 inside the helmet; other pressure increments were made to keep respiratory rate <20 breaths per min and minimising, by visual inspection, the occurrence of accessory muscle recruitment. The fastest rate of pressurisation and a cycling-off flow threshold from 25% to 50% of the peak inspiratory flow were also set. Further changes were eventually made according to ABGs.	Facemask NIV	Facemask NIV (The ventilator settings were decided according to the usual practice: maximal tolerated inspiratory pressure to obtain a tidal volume of 6–8 mL·kg-1 of body weight and PEEP between 3 and 5 cmH2O)	80	History of COPD and acute hypoxic respiratory failure as defined by the study protocol admitted to the ICU	Intubation Rate, Complications, Patient Comfort

Vargas et al.	2009	France	Helmet NIV (CaStar)	Pressure support was adjusted initially during 5 minutes of noninvasive ventilation with the facemask, before starting the recordings. The level of pressure support was increased gradually until the expired tidal volume (VT) was 6 to 8 mL/kg of body weight. PEEP was set at 4 to 5 cm H2O.	Facemask NIV	Facemask NIV (set same way as helmet group)	11	Patients intubated for more than 48 hours who tolerated spontaneous breathing trial after recovery from acute disease	Patient Comfort
Yang et al.	2015	China	Helmet CPAP (CaStar)	The FiO2 was adjusted to 40–50%, and PEEP was adjusted to 8–10 cm H2O in order to maintain pulse oxygen saturation (SpO2)>95%.	Facemask NIV	Facemask NIV (initial parameters: inspiration pressure [IPAP], 10–20 cm H2O; expiration pressure [EPAP], 0–4 cm H2O; FIO2, 60–100%; inspiration: expiration, 1:1.5 to 1:2; and time for pressure increase, 0.5–1 s). All these parameters were adjusted gradually according to the clinical outcomes and patient tolerance)	40	Patients who underwent surgery for Stanford type A aortic dissection and had acute respiratory failure as per study protocol	Intubation Rate, Mortality, ICU length of Stay, Hospital Length of Stay, Duration of Mechanical Ventilation, Complications

Table 2: Complications of NIV

Author	Definition of Complication	Complications in Helmet Group	Complication in Comparator Group	Scale Used	Comfort Score in Helmet Group (mean, SD)	Comfort Score in Comparator Group (mean, SD)
Adi et al.	Not Recorded	Not Recorded	Not Recorded	Likert score (mean rank)	2	2
Adi and Salleh	Not Recorded	Not Recorded	Not Recorded	Likert score (mean rank)	67.8	55.7
Ali et al.	Erythema and Pressure Sores	0 of 15	1 of 15	HUS (1h and 2h)	3.5 (0.6) and 3.2 (0.7)	2.6 (0.9) and 2.2 (0.7)
Antogalia et al.	Metabolic complications; sepsis and pneumonia; tracheostomy	4/20; 2/20; 0/20	3/20; 4/20; 1/20	Not Recorded	Not Recorded	Not Recorded
Cakir Gurbuz et al.	Face laceration, Erythema, Axillary erythema, and Laceration	9/25	14/23	Not Recorded	Not Recorded	Not Recorded
Fasano et al.	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded
Grieco et al.	Not Recorded	Not Recorded	Not Recorded	Dyspnea VAS	3 (2.2)	8 (2.2)
Grieco et al	VAP, barotrauma	14/54 and 2/54	18/55 and 2/55	Dyspnea VAS	1.9 (2.0)	2.5 (2.2)
Liu et al.	Total and Skin Lesions	3/15 and 9/15	8/15 and 4/15	Not Recorded	Not Recorded	Not Recorded
Liu et al.	Skin lesion and Gastric Distension	2/29 and 0/29	0/30 and 1/30	Not Recorded	Not Recorded	Not Recorded
Longhini et al.	Not Recorded	Not Recorded	Not Recorded	0 to 10 scale with 0 being least comfortable	7 (1.5)	5 (0.4)
Navalesi et al.	Not Recorded	Not Recorded	Not Recorded	1 to 5 scale with 1 being least comfortable	3 (1.5)	3 (0.8)
Patel et al.	Mask Deflation and Skin Ulceration	2/44 and 3/44	0/39 and 3/39	Not Recorded	Not Recorded	Not Recorded
Pisani et al.	Noise; claustrophobia; gastric distension; vomit; sweat; tightness	4/39; 2/29; 2/39; 0/39; 0/39; 3/39	0/44; 1/44; 2/44; 1/44; 0/44; 5/44	Dyspnea VAS (at 2 hours)	4.3 (2.1)	3.3 (2.0)
Vargas et al.	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded
Yang et al.	Skin lesions and Gastric distension	0/20 and 0/20	7/20 and 5/20	Not Recorded	Not Recorded	Not Recorded
Alharthy et al.	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded
Antonelli et al.	Skin Necrosis, Gastric Distension, and Eye Irritation Cumulative	0/33; 0/33; 0/33	7/10; 3/66; 4/66	Not Recorded	Not Recorded	Not Recorded
Antonelli et al.	Skin Breakdown; Conjunctivitis; Gastric Distension; Intolerance; DVT; Total	0/33; 0/33; 0/33; 0/33; 1/33; 0/33	4/33; 2/33; 0/33; 6/33; 0/33; 12/33	Not Recorded	Not Recorded	Not Recorded
Conti et al.	Skin Necrosis and VAP	1/25 and 1/25	1/25 and 7/25	Not Recorded	Not Recorded	Not Recorded
Gaulton et al.	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded
Giovini et al.	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded
Principi et al.	Skin Necrosis, Gastric Distension, Eye Irritation	0/17; 0/17; 0/17	2/17; 0/17; 2/17	Not Recorded	Not Recorded	Not Recorded
Rocco et al.	Total; Skin Necrosis; Gastric Distension	6/19; 2;/19; 0/19	10/17; 9/17; 1;17	Not Recorded	Not Recorded	Not Recorded

Figure 1: Prisma Study Flow

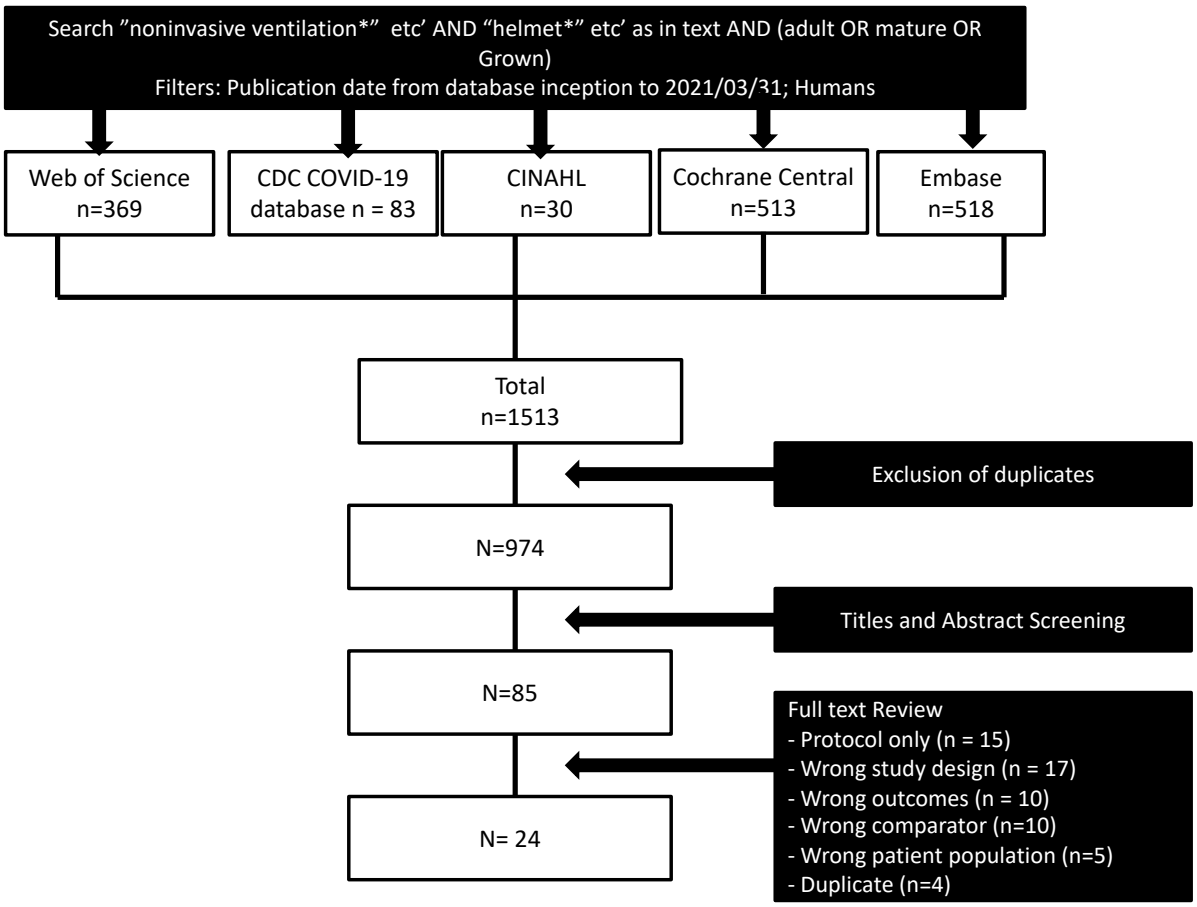


Figure 2: Effect of helmet NIV compared to facemask NIV on mortality. RCT data only. DF = degrees of freedom.

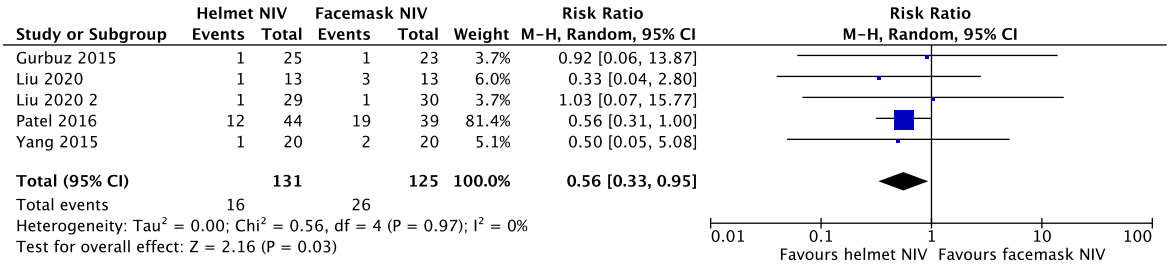


Figure 3: Effect of helmet NIV compared to facemask NIV on intubation. RCT data only. Studies subdivided by type of respiratory failure. DF = degrees of freedom.

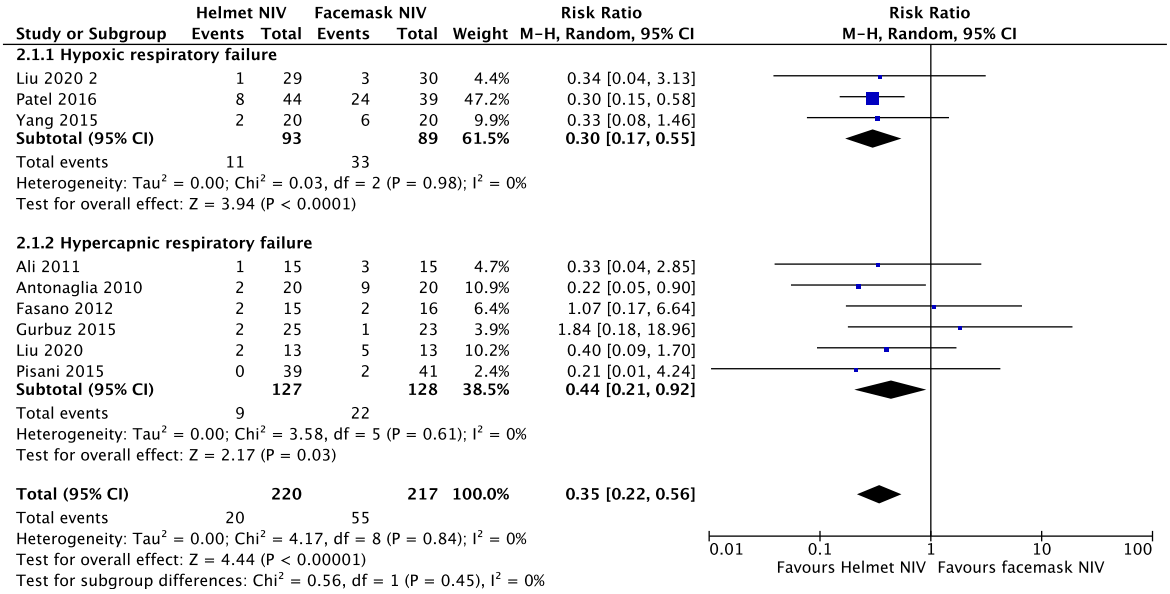


Figure 4: Effect of helmet NIV compared to facemask NIV on ICU length of stay. RCT data only. Df = degrees of freedom

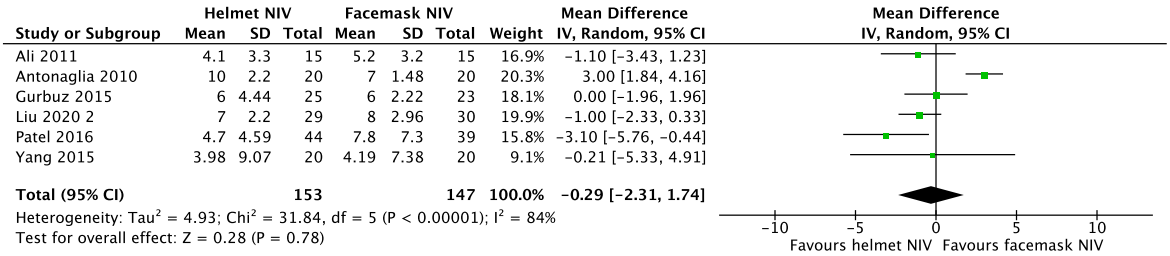


Figure 5: Effect of helmet NIV compared to facemask NIV on duration of NIV. RCT data only. Df = degrees of freedom

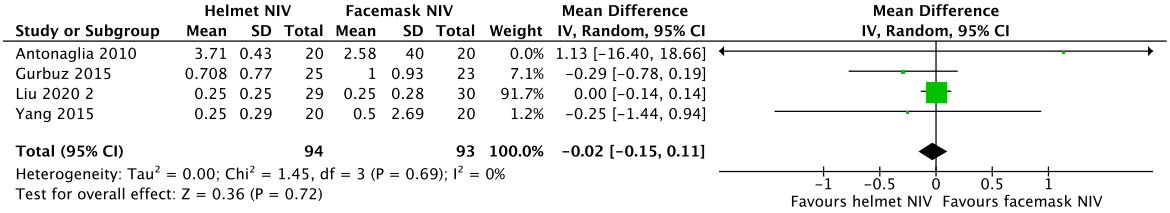


Figure 6: Effect of helmet NIV compared to high flow nasal cannula on intubation. RCT data only. Df = degrees of freedom

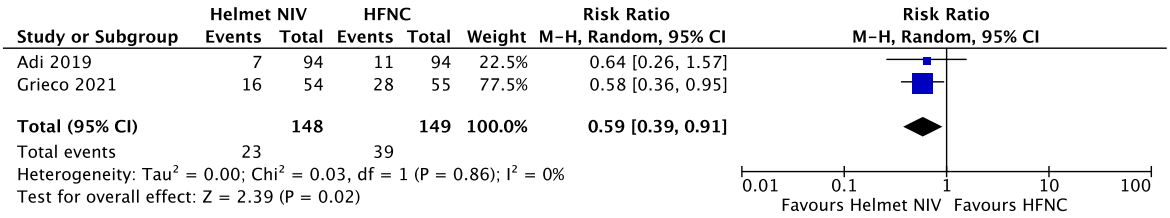
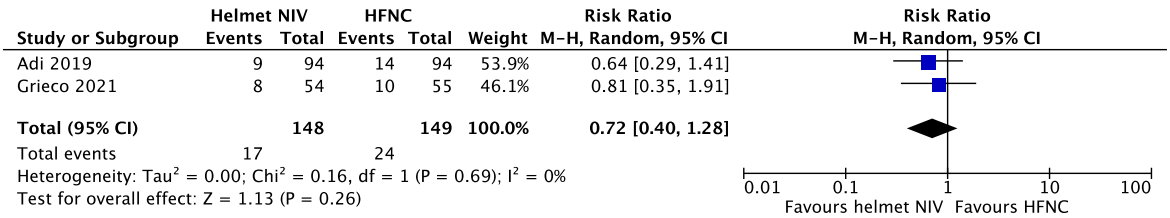
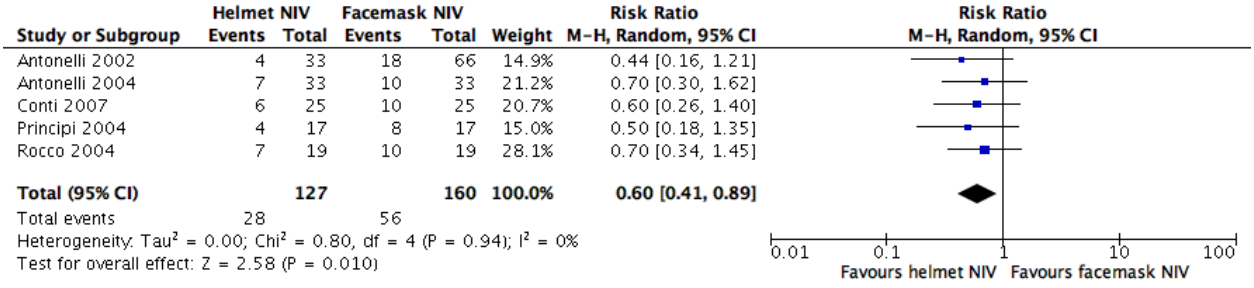


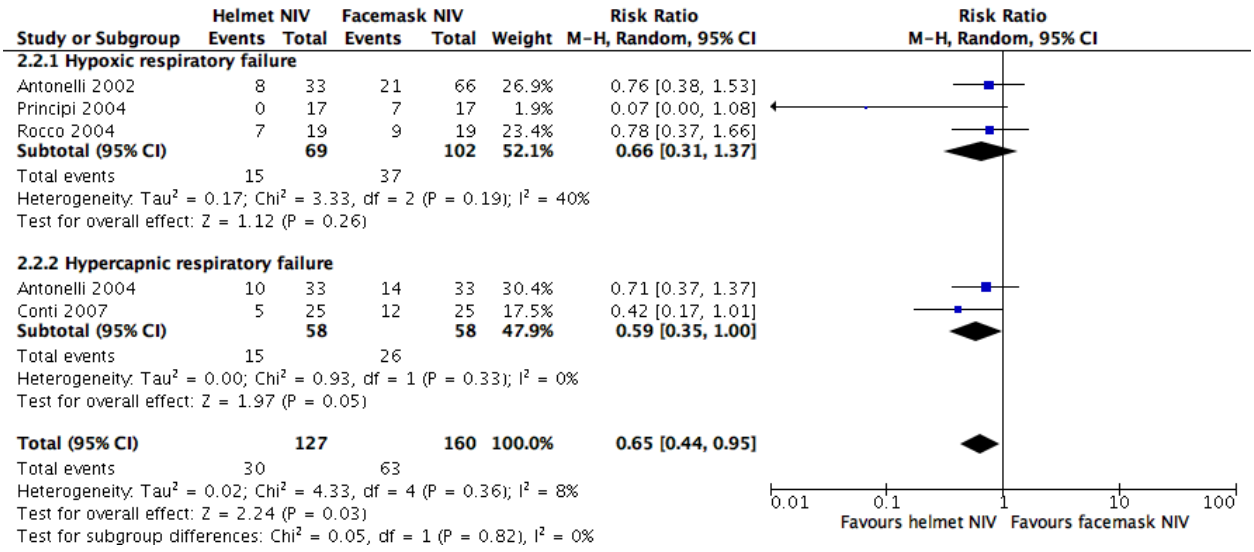
Figure 7: Effect of helmet NIV compared to high flow nasal cannula on mortality. RCT data only. Df = degrees of freedom



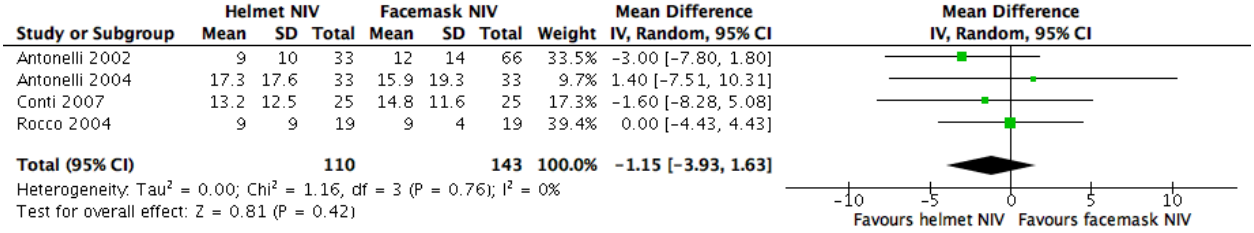
e-Figure 1: Effect of helmet NIV compared to facemask NIV on mortality. Observational data only. Df = degrees of freedom



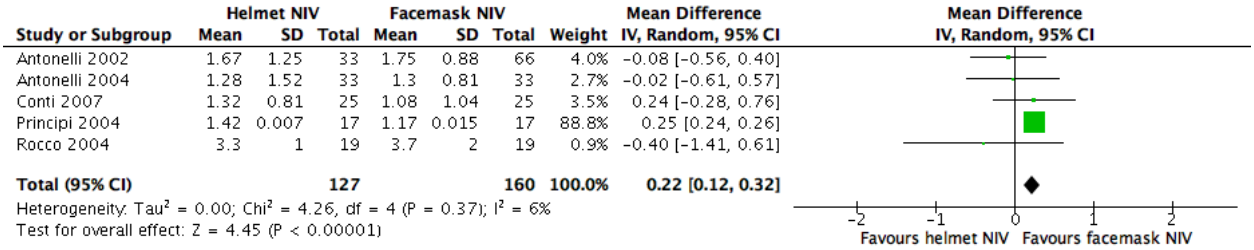
e-Figure 2: Effect of helmet NIV compared to facemask NIV on intubation. Observational data only. Studies are grouped by type of respiratory failure. Df = degrees of freedom



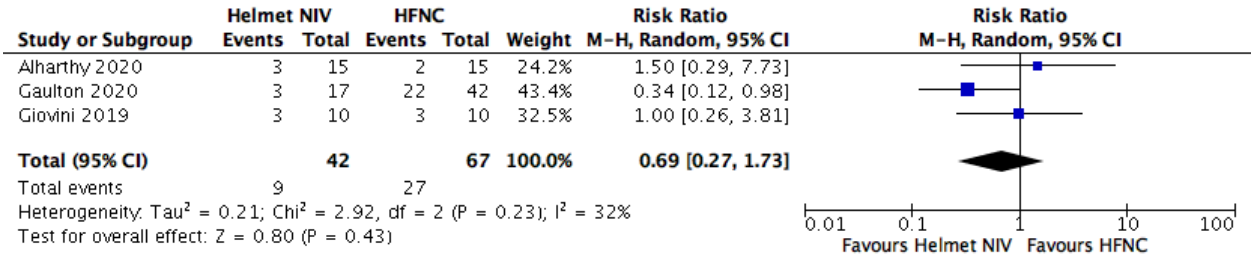
e-Figure 3: Effect of helmet NIV compared to facemask NIV on ICU length of stay. Observational data only. Df = degrees of freedom



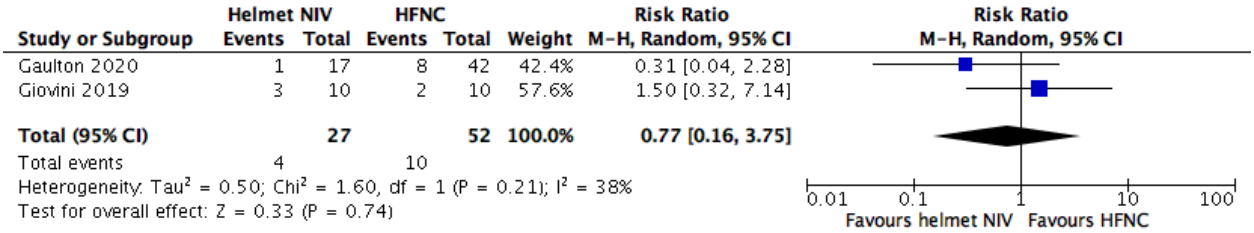
e-Figure 4: Effect of helmet NIV compared to facemask NIV on duration of NIV. Observational data only. Df = degrees of freedom



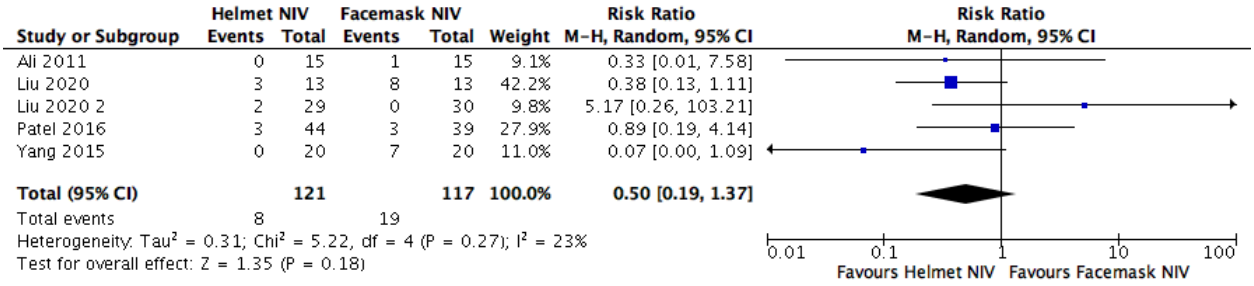
e-Figure 5: Effect of helmet NIV compared to high flow nasal cannula on intubation. Observational data only. Df = degrees of freedom



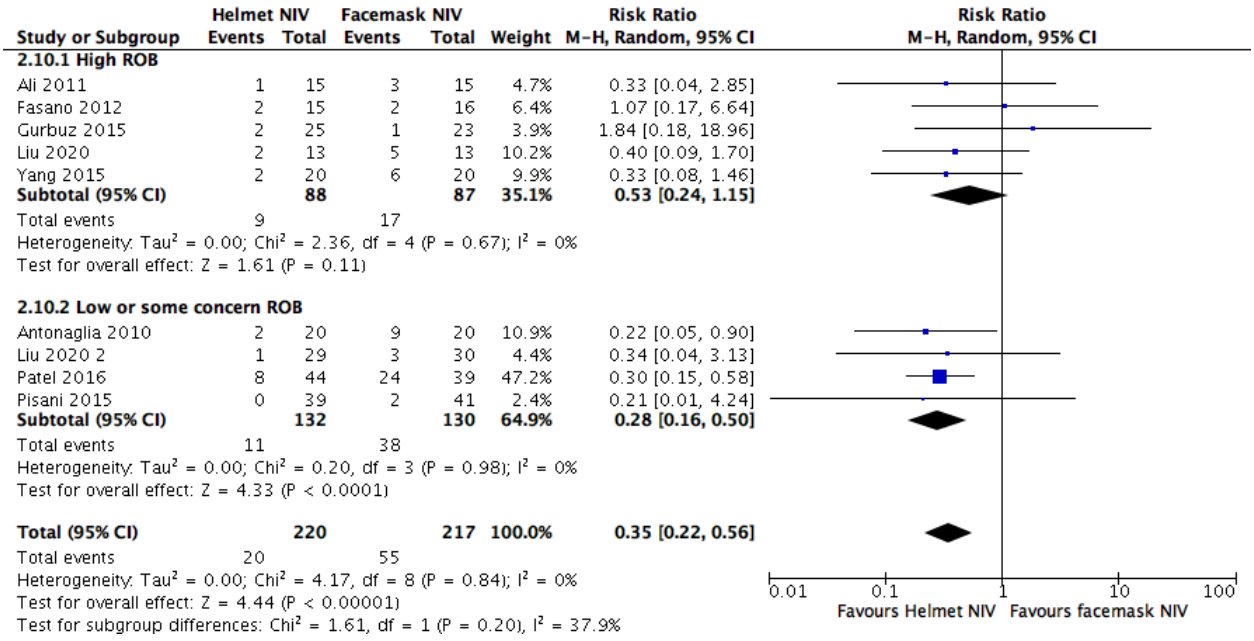
e-Figure 6: Effect of helmet NIV compared to high flow nasal cannula on mortality. Observational data only. Df = degrees of freedom



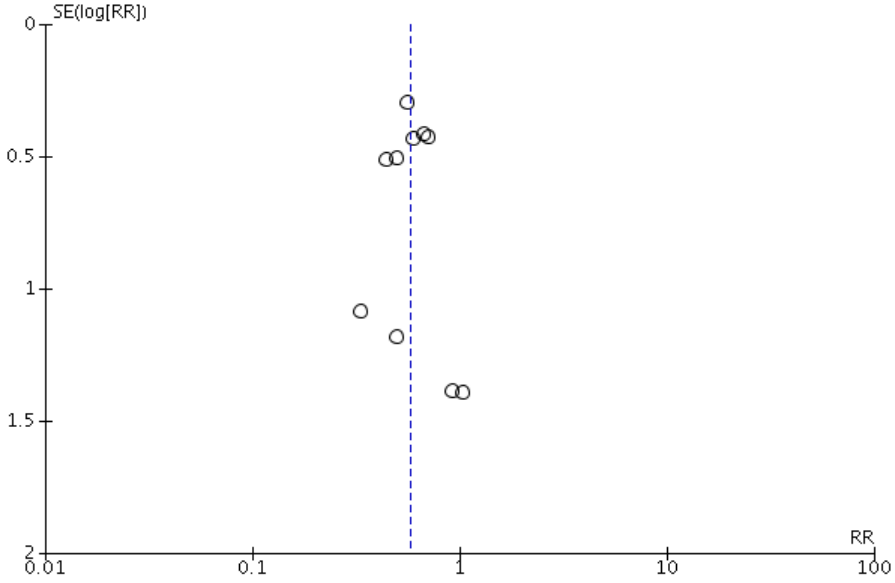
e-Figure 7: Effect of helmet NIV compared to facemask NIV on facial pressure sores. RCT data only. Df = degrees of freedom



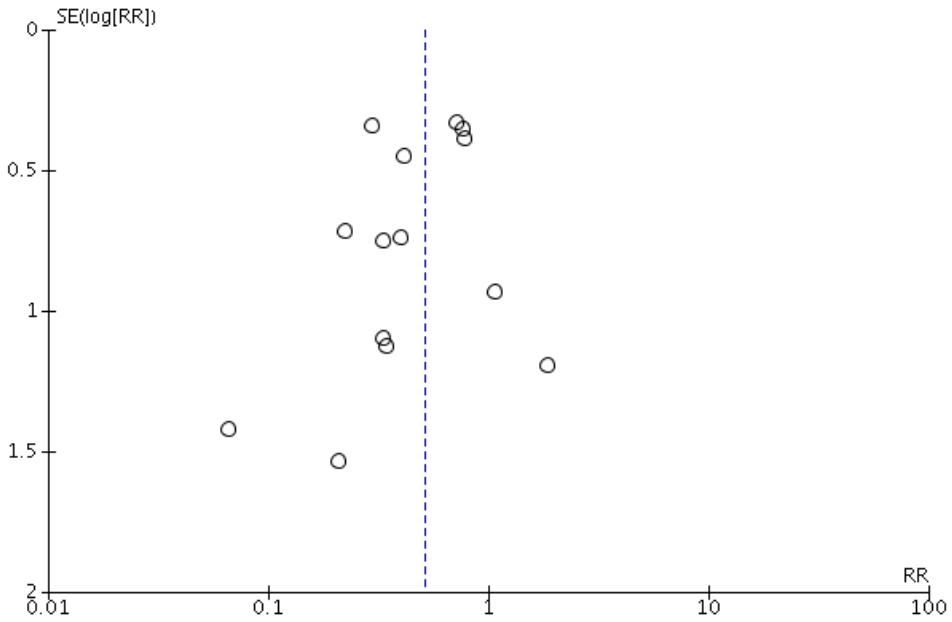
e-Figure 8: Effect of helmet NIV compared to facemask NIV on intubation. Studies are group by risk of bias. RCT data only. Df = degrees of freedom



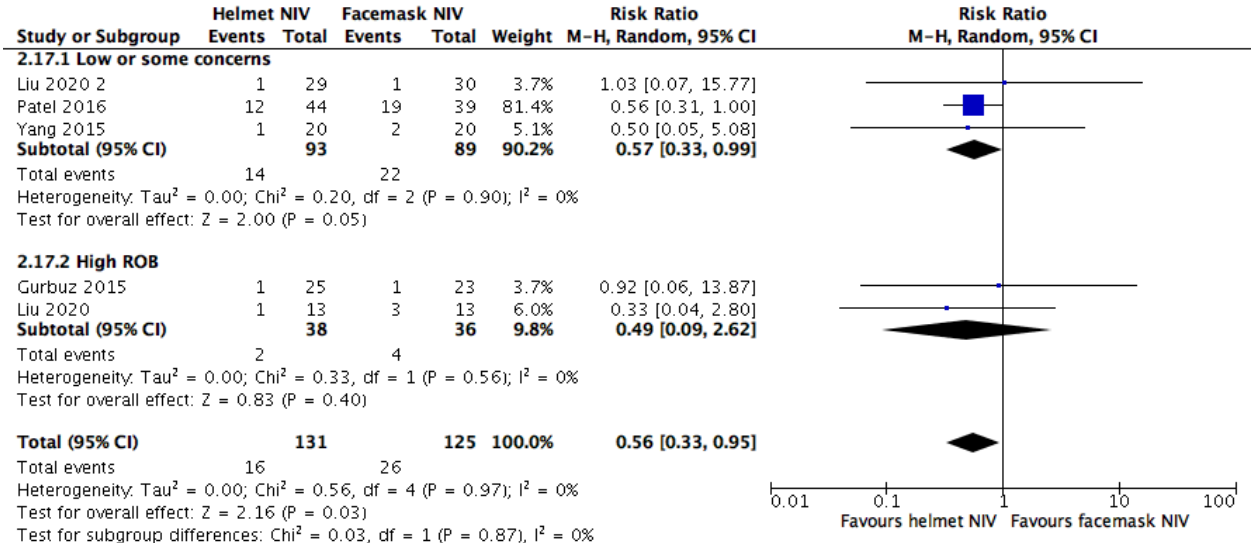
e-Figure 9: Funnel plot of helmet NIV compared to facemask NIV for the outcome of mortality



e-Figure 10: Funnel plot of helmet NIV compared to facemask NIV for the outcome of intubation



e-Figure 11: Effect of helmet NIV compared to facemask NIV on mortality. Studies are group by risk of bias. RCT data only. Df = degrees of freedom



Supplementary Table 1: PRISMA checklist

	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Supplementary materials
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9

Supplementary Table 1: PRISMA checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Supplementary Table 2A: Risk of bias for RCTs for outcome of mortality

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias for the outcome of Mortality
Adi, 2019	Some concerns	High	Low	Low	Some concerns	High
Gurbuz, 2015	Some concerns	High	Low	Low	Some concerns	High
Grieco, 2021	Low	Low	Low	Low	Low	Low
Liu 2020	Some concerns	Low	Low	Low	Some concerns	High
Patel 2016	Low	Low	Low	Low	Low	Low
Liu 2020 (2)	Low	Low	Low	Low	Low	Low
Yang 2015	Low	Low	Low	Low	Some concerns	Some concerns

Supplementary Table 2b: Risk of bias for observational studies

Study	Selection	Comparability	Outcome/Exposure
Alharthy, 2020	****	-	***
Antonelli, 2002	****	**	***
Antonelli, 2004	****	**	***
Conti, 2007	****	**	***
Gaulton, 2020	***	-	***
Giovini, 2019	****	**	***
Principi, 2004	****	**	***
Rocco, 2004	****	**	***

Supplementary Table 2c: Risk of bias for RCTs for outcome of intubation

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias for the outcome of Intubation
Adi, 2019	Some concerns	High	Low	Low	Some concerns	High
Ali, 2011	Some concerns	High	Low	Low	Some concerns	High
Antogalia, 2010	Low	Low	Low	Low	Some concerns	Some concerns
Gurbuz, 2015	Some concerns	High	Low	Low	Some concerns	High
Fasano, 2012	Some concerns	High	Low	Low	Some concerns	High

Grieco, 2021	Low	Low	Low	Low	Low	Low
Liu 2020	Some concerns	Low	Low	Low	Some concerns	High
Patel 2016	Low	Low	Low	Low	Low	Low
Pisani 2015	Low	Low	Low	Low	Low	Low
Liu 2020 (2)	Low	Low	Low	Low	Low	Low
Yang 2015	Some concerns	Low	Low	Low	Some concerns	High

Supplementary Table 3: GRADE Summary of Findings Table

Question: Helmet NIV compared to facemask NIV for respiratory failure

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Helmet NIV	oronasal NIV	Relative (95% CI)	Absolute (95% CI)		
Mortality (RCT)												
5	randomised trials	not serious	not serious	not serious	very serious [a]	none	16/131 (12.2%)	26/125 (20.8%)	**RR 0.56** (0.33 to 0.95)	**92 fewer per 1,000** (from 139 fewer to 10 fewer)	⨁⨁◯◯ LOW	CRITICAL
Intubation (RCT)												
9	randomised trials	serious [b]	not serious	not serious	serious [a]	none	20/220 (9.1%)	55/217 (25.3%)	**RR 0.35** (0.22 to 0.56)	**165 fewer per 1,000** (from 198 fewer to 112 fewer)	⨁⨁◯◯ LOW	CRITICAL
ICU LOS (RCT)												
6	randomised trials	serious [b]	serious [c]	not serious	serious [a]	none	153	147	-	MD **0.29 lower** (2.31 lower to 1.74 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Duration of NIV (RCT)												
4	randomised trials	serious [b]	not serious	not serious	serious [a]	none	94	93	-	MD **0.02 lower** (0.15 lower to 0.11 higher)	⨁⨁◯◯ LOW	IMPORTANT
Pressure sores (RCT)												
5	randomised trials	serious [b]	not serious	not serious	very serious [a,d]	none	8/121 (6.6%)	19/117 (16.2%)	**RR 0.50** (0.19 to 1.37)	**81 fewer per 1,000** (from 132 fewer to 60 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Intubation (observational studies)												
5	observational studies	not serious	not serious	not serious	serious [a]	none	30/127 (23.6%)	63/160 (39.4%)	**RR 0.65** (0.44 to 0.95)	**138 fewer per 1,000** (from 221 fewer to 20 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality (observational studies)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Helmet NIV	oronasal NIV	Relative (95% CI)	Absolute (95% CI)		
5	observational studies	not serious	not serious	not serious	serious [a]	none	27/127 (21.3%)	55/160 (34.4%)	**RR 0.59** (0.40 to 0.88)	**141 fewer per 1,000** (from 206 fewer to 41 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
ICU LOS (observational studies)												
4	observational studies	not serious	not serious	not serious	very serious [a,d]	none	110	143	-	MD **1.15 lower** (3.93 lower to 1.63 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Duration of NIV (Observational studies)												
5	observational studies	not serious	not serious	not serious	serious [a]	none	127	160	-	MD **0.22 higher** (0.12 higher to 0.32 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. very low event numbers which are far below optimal information size
b. high proportion of the included studies have high ROB
c. High I squared with variable effects across studies
d. wide confidence intervals that don't exclude serious benefit or harm

Question: Helmet NIV compared to HFNC for respiratory failure

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Helmet NIV	HFNC	Relative (95% CI)	Absolute (95% CI)		
Mortality (RCTs)												
2	randomised trials	serious [a]	not serious	not serious	very serious [b,c]	none	17/148 (11.5%)	24/149 (16.1%)	**RR 0.72** (0.40 to 1.28)	**45 fewer per 1,000** (from 97 fewer to 45 more)	⨁◯◯◯ VERY LOW	CRITICAL
Intubation (RCTs)												
2	randomised trials	serious [a]	not serious	not serious	serious [c]	none	23/148 (15.5%)	39/149 (26.2%)	**RR 0.59** (0.39 to 0.91)	**107 fewer per 1,000** (from 160 fewer to 24 fewer6)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Helmet NIV	HFNC	Relative (95% CI)	Absolute (95% CI)		
Mortality (Observational studies)												
2	observational studies	not serious	not serious	not serious	serious [b,c]	none	4/27 (14.8%)	10/52 (19.2%)	**RR 0.77** (0.16 to 3.75)	**44 fewer per 1,000** (from 162 fewer to 529 more)	⨁◯◯◯ VERY LOW	CRITICAL
Intubation (Observational studies)												
3	observational studies	not serious	not serious	not serious	serious [b]	none	9/42 (21.4%)	27/67 (40.3%)	**RR 0.69** (0.27 to 1.73)	**125 fewer per 1,000** (from 294 fewer to 294 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. One out of two included studies have high ROB
b. wide confidence intervals that do not exclude serious benefit or harm
c. very low event numbers which are far below optimal information size as only two small studies are included.

Supplementary Table 4: Characteristics of Included Cohort and Case Series Studies

Author	Year	Country	Type of Helmet	Settings Used for Helmet	Comparator	Settings Used for Comparator	Total (n)	Select Inclusion Criteria	Outcomes
Alharthy et al.	2020	Saudi Arabia	H-CPAP	CPAP at high flow rates to prevent rebreathing (median flow rate 45 L/min) with a median fraction of inspired oxygen of 40%.	High Flow Nasal Canula	Adjusted at a median flow rate of 60 L/min and median fraction of inspired oxygen of 40%.	30	Adult patients with confirmed COVID-19 requiring higher support than standard oxygen	Intubation Rate
Antonelli et al.	2002	Italy	H-NIV (CaStar)	Once the helmet was positioned, pressure support was increased in increments of 2–3 cm H2O to obtain the patient comfort, a respiratory rate lower than 25 breaths/min, and the disappearance of accessory muscle activity (as evaluated by palpating the sternocleidomastoid muscle). PEEP was increased in increments of 2–3 cm H2O up to 10–12 cm H2O to assure a peripheral oxygen saturation of at least 92% with the lowest FIO2 possible.	Facemask NIV	Not Described	99	Non-COPD patients with acute respiratory failure as defined by study protocol	Intubation Rate, Mortality, ICU Length of Stay, Duration of Mechanical Ventilation, Complications
Antonelli et al.	2004	Italy	H-NIV (CaStar)	After the mask was secured, the initial level of 10 cmH2O pressure support was gradually increased in increments of 2–3 cmH2O to obtain a respiratory rate of less than 25 breaths/min, disappearance of accessory muscle activity (evaluated by palpating the sternocleidomastoid muscle),12 and patient comfort. PEEP was set at5–7 cmH2O to counterbalance the intrinsic PEEP level.	Facemask NIV	Not Described	66	Patients with acute decompensation of COPD eligible for treatment with NPPV admitted to ICU	Intubation Rate, Mortality, ICU Length of Stay, Duration of Mechanical Ventilation, Complications
Conti et al.	2007	Italy	H-NIV (CaStar)	Started with 10 cm H2O of pressure support, with progressive stepwise increase of 2-3 cm H2O, according to patient comfort, to obtain a respiratory rate 25 breaths/min and the disappearance of accessory muscle activity or paradoxical abdominal motion. Positive end-expiratory pressure (PEEP) was increased in steps of 2–3 cm H2O, up to a maximum of 12 cm H2O, to maintain the arterial oxygen saturation over 90% with the lowest possible FIO2.	Facemask NIV	Not Described	50	Patients who developed post operative acute respiratory failure after abdominal surgery admitted to the ICU	Intubation Rate, Mortality, ICU Length of Stay, Duration of Mechanical Ventilation, Complications
Gaulton et al.	2020	USA	H-CPAP SeaLong	CPAP between 5 - 10 cm H2O and FiO2 titrated to keep >92%.	High Flow Nasal Canula	HFNC was adjusted at a median flow rate of 60 L/min and median fraction of inspired oxygen of 40%.	59	Patients with body mass index greater than or equal to 25 kg/m2 and were candidates for non-invasive respiratory support as per study protocol	Intubation Rate, Mortality
Giovini et al.	2019	Italy	H-CPAP	Not Described	High Flow Nasal Canula	Not Described	20	Patients with moderate ARDS as defined y Berlin criteria	Intubation Rate, Mortality

Principi et al.	2004	Italy	H-CPAP (CaStar)	High-flow CPAP (Vital Signs, Brighton, UK) was set at 8 cmH2O with FIO2 0.6 controlled by means of an oximeter (Miniox II Oxygen Monitor, Catalyst Research Owings Mills, Md., USA).	Facemask CPAP	Facemask CPAP (same settings as helmet group)	34	Patients presenting with dyspnea, tachypnea, use of accessory muscles, and paradoxical abdominal motion, with infiltrates on chest radiography	intubation Rate, Mortality, Duration of Mechanical Ventilation, Complications
Rocco et al.	2004	Italy	H-NIV (CaStar)	The ventilator was set with pressure support of 10 cm H2O, and the level of pressure support was progressively increased in increments of 2 to 3 cm H2O to obtain patient comfort, an RR 25 breaths/min, and the disappearance of accessory muscle activity. Positive end-expiratory pressure (PEEP) was increased by 2 to 3 cm H2O, up to a maximum level of 12 cm H2O to maintain the arterial oxygen saturation 90% with the lowest Fio2 possible.	Facemask NIV	Facemask NIV (same settings as helmet group)	38	Immunocompromised patients with hypoxemic acute respiratory failure and pulmonary infiltrates admitted to ICU	Intubation Rate, Mortality, ICU Length of Stay, Duration of Mechanical Ventilation, Complications

Non-Invasive Ventilation (NIV) Helmet – SR – Literature Search

Research Question(s)

1. In all patients with acute respiratory failure, does the use of helmet NIV reduce mortality, intubation rate and days of MV compared to oro-nasal NIV and high flow nasal cannula (HFNC).
   Patient – All adult patients acute with respiratory failure of any type or etiology
   Intervention – NIV delivered by helmet interface
   Control – Oro-nasal NIV or high flow nasal cannula
   Outcome – mortality, intubation, invasive mechanical ventilator free days, duration of mechanical ventilation, duration of NIV, ICU length of stay, hospital length of stay, patient comfort and adverse events
      -for mortality, we will capture closest to 30 days or if not available, hospital mortality
      -for intubation, we will capture any need for intubation during index hospitalization

Seed Articles:

- Ferreyro BL, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. JAMA. 2020 Jul 7;324(1):57-67. https://pubmed.ncbi.nlm.nih.gov/32496521/
- Patel BK, et al. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA. 2016;315(22):2435-2441. https://pubmed.ncbi.nlm.nih.gov/27179847/

Search by: Kaitryn Campbell (kcampbel@stjosham.on.ca)
Requestor: Dipayan Chaudhuri (dipayan.chaudhuri@medportal.ca)
Date(s): 2020 Oct 23
Limits: NOT case reports; Human NOT Animal
Databases: Ovid Medline [ppez] & Embase [oemezd]; Web of Science; The Cochrane Library; International HTA database (https://database.inahta.org/); EBSCO CINAHL Complete; LILACS; WHO COVID-19 Global literature on coronavirus disease (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/)
Filters: None
Output: RIS (931 results total after duplicates removed)

Concept #1: Noninvasive Ventilation, etc.
Noninvasive Ventilation/
Oxygen Inhalation Therapy/ use ppez
Oxygen Therapy/ use oemezd
((non-invasive* OR noninvasive*) ADJ3 (oxygen* OR O2 OR ventilat*)).tw,kf,kw.

Respiratory Insufficiency/ use ppez
Respiratory Distress Syndrome, Adult/ use ppez
Respiratory Failure/ use oemezd
Acute Respiratory Failure/ use oemezd
Adult Respiratory Distress Syndrome/ use oemezd

((lung? OR respiratory OR respiration OR pulmonary OR ventilator?) ADJ2 (depress* OR insufficien* OR fail* OR deficien* OR disturb* OR dysfunction* OR compromis*)).tw,kf,kw.
(((acute OR adult*) ADJ respiratory distress) OR ARDS OR ARDSS).tw,kf,kw.

Continuous Positive Airway Pressure/ use ppez
Positive End Expiratory Pressure/ use oemezd
(continuous positive airway pressure OR CPAP OR nCPAP OR CPPB OR CPPV OR continuous positive pressure ventilation OR CPPV OR airway pressure release ventilation OR APRV OR ((bi-level OR bilevel) ADJ2 positive airway pressure) OR (hyperbaric ADJ (respiration OR ventilation)) OR (positive pressure ADJ (breathing OR respiration OR ventilation)) OR positive endexpiratory pressure breathing OR PEEP).tw,kf,kw.
å
Concept #2: Helmet
Head Protective Devices/ use ppez
exp Helmet/ use oemezd
helmet*.tw,kf,kw.

exp animals/
exp animal experimentation/ OR exp animal experiment/
exp models animal/
nonhuman/
exp vertebrate/ OR exp vertebrates/
or/
exp humans/
exp human experimentation/ OR exp human experiment/
or/
25 not 28

(Case Reports.pt. OR *Case Report/) NOT (case series.ti. AND (Case Reports.pt. OR *Case Report/))

Ovid
Database(s): **Embase** 1974 to 2020 October 22, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

#	Searches	Results
1	Noninvasive Ventilation/	12868
2	Oxygen Inhalation Therapy/ use ppez	14575
3	Oxygen Therapy/ use oemezd	30522
4	((non-invasive* or noninvasive*) adj3 (oxygen* or O2 or ventilat*)).tw,kf,kw.	25627
5	Respiratory Insufficiency/ use ppez	32369
6	Respiratory Distress Syndrome, Adult/ use ppez	19909
7	Respiratory Failure/ use oemezd	68775
8	Acute Respiratory Failure/ use oemezd	12805
9	Adult Respiratory Distress Syndrome/ use oemezd	39543

10	((lung? or respiratory or respiration or pulmonary or ventilator?) adj2 (depress* or insufficien* or fail* or deficien* or disturb* or dysfunction* or compromis*)).tw,kf,kw.	180943
11	(((acute or adult*) adj respiratory distress) or ARDS or ARDSS).tw,kf,kw.	61262
12	Continuous Positive Airway Pressure/ use ppez	7288
13	Positive End Expiratory Pressure/ use oemezd	55218
14	(continuous positive airway pressure or CPAP or nCPAP or CPPB or CPPV or continuous positive pressure ventilation or CPPV or airway pressure release ventilation or APRV or ((bi-level or bilevel) adj2 positive airway pressure) or (hyperbaric adj (respiration or ventilation)) or (positive pressure adj (breathing or respiration or ventilation)) or positive endexpiratory pressure breathing or PEEP).tw,kf,kw.	64104
15	or/1-14 [Noninvasive Ventilation, etc. Concept]	408808
16	Head Protective Devices/ use ppez	3598
17	exp Helmet/ use oemezd	5703
18	helmet*.tw,kf,kw.	12414
19	or/16-18 [Helmet Concept]	14658
20	exp animals/	49787816
21	exp animal experimentation/ or exp animal experiment/	2630293
22	exp models animal/	2002835
23	nonhuman/	6362133
24	exp vertebrate/ or exp vertebrates/	48451569
25	or/20-24	51664560
26	exp humans/	40330743
27	exp human experimentation/ or exp human experiment/	534778
28	or/26-27	40333169
29	25 not 28	11333047
30	15 and 19 [Noninvasive Ventilation, etc.+ Helmet]	670
31	30 not 29 [Noninvasive Ventilation, etc.+ Helmet, Human NOT Animal Filter applied]	652
32	(Case Reports.pt. or *Case Report/) not (case series.ti. and (Case Reports.pt. or *Case Report/))	2144091
33	31 not 32 [Noninvasive Ventilation, etc.+ Helmet, Human NOT Animal Filter applied, Case Reports removed]	622
34	remove duplicates from 33 [Final results, Human NOT Animal, Case Reports & duplicates removed]	426

Web of Science

Set	Results	Search Terms
# 25	326	#24 AND #18 Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=All years
# 24	9,501	#23 OR #22 OR #21 OR #20 OR #19
# 23	2,041	AK=helmet*
# 22	6,684	AB=helmet*
# 21	3,996	TI=helmet*
# 20	9,296	TS=helmet*
# 19	331	TS=Head Protective Devices
# 18	112,258	#17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
# 17	5,966	AK=(continuous positive airway pressure OR CPAP OR nCPAP OR CPPB OR CPPV OR continuous positive pressure ventilation OR CPPV OR airway pressure release ventilation OR APRV OR ((bi-level OR bilevel) NEAR/2 positive airway pressure) OR (hyperbaric NEAR/1 (respiration OR ventilation)) OR (positive pressure NEAR/1 (breathing OR respiration OR ventilation)) OR positive endexpiratory pressure breathing OR PEEP)
# 16	17,782	AB=(continuous positive airway pressure OR CPAP OR nCPAP OR CPPB OR CPPV OR continuous positive pressure ventilation OR CPPV OR airway pressure release ventilation OR APRV OR ((bi-level OR bilevel) NEAR/2 positive airway pressure) OR (hyperbaric NEAR/1 (respiration OR ventilation)) OR (positive pressure NEAR/1 (breathing OR respiration OR ventilation)) OR positive endexpiratory pressure breathing OR PEEP)
# 15	12,327	TI=(continuous positive airway pressure OR CPAP OR nCPAP OR CPPB OR CPPV OR continuous positive pressure ventilation OR CPPV OR airway pressure release ventilation OR APRV OR ((bi-level OR bilevel) NEAR/2 positive airway pressure) OR (hyperbaric NEAR/1 (respiration OR ventilation)) OR (positive pressure NEAR/1 (breathing OR respiration OR ventilation)) OR positive endexpiratory pressure breathing OR PEEP)
# 14	10,459	TS=Continuous Positive Airway Pressure
# 13	8,234	AK=(((acute OR adult*) NEAR/1 respiratory distress) OR ARDS OR ARDSS)
# 12	16,163	AB=(((acute OR adult*) NEAR/1 respiratory distress) OR ARDS OR ARDSS)
# 11	12,237	TI=(((acute OR adult*) NEAR/1 respiratory distress) OR ARDS OR ARDSS)
# 10	7,119	AK=((lung? OR respiratory OR respiration OR pulmonary OR ventilator?) NEAR/2 (depress* OR insufficien* OR fail* OR deficien* OR disturb* OR dysfunction* OR compromis*))
# 9	44,619	AB=((lung? OR respiratory OR respiration OR pulmonary OR ventilator?) NEAR/2 (depress* OR insufficien* OR fail* OR deficien* OR disturb* OR dysfunction* OR compromis*))
# 8	15,389	TI=((lung? OR respiratory OR respiration OR pulmonary OR ventilator?) NEAR/2 (depress* OR insufficien* OR fail* OR deficien* OR disturb* OR dysfunction* OR compromis*))
# 7	7,886	TS=Respiratory Distress Syndrome, Adult
# 6	6,679	TS=Respiratory Insufficiency
# 5	3,255	AK=((non-invasive* OR noninvasive*) NEAR/3 (oxygen* OR O2 OR ventilat*))
# 4	6,556	AB=((non-invasive* OR noninvasive*) NEAR/3 (oxygen* OR O2 OR ventilat*))
# 3	5,713	TI=((non-invasive* OR noninvasive*) NEAR/3 (oxygen* OR O2 OR ventilat*))
# 2	1,211	TS=Oxygen Inhalation Therapy
# 1	8,419	TS=Noninvasive Ventilation

The Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Noninvasive Ventilation] this term only	241
#2	MeSH descriptor: [Oxygen Inhalation Therapy] this term only	1157
#3	((non-invasive* OR noninvasive*) NEAR3 (oxygen* OR O2 OR ventilat*)):ti,ab,kw	0
#4	MeSH descriptor: [Respiratory Insufficiency] this term only	1577
#5	((lung? OR respiratory OR respiration OR pulmonary OR ventilator?) NEAR2 (depress* OR insufficien* OR fail* OR deficien* OR disturb* OR dysfunction* OR compromis*)):ti,ab,kw OR (((acute OR adult*) NEXT respiratory distress) OR ARDS OR ARDSS):ti,ab,kw	2826
#6	MeSH descriptor: [Continuous Positive Airway Pressure] this term only	1074
#7	(continuous positive airway pressure OR CPAP OR nCPAP OR CPPB OR CPPV OR continuous positive pressure ventilation OR CPPV OR airway pressure release ventilation OR APRV OR ((bi-level OR bilevel) NEAR2 positive airway pressure) OR (hyperbaric NEXT (respiration OR ventilation)) OR (positive pressure NEXT (breathing OR respiration OR ventilation)) OR positive endexpiratory pressure breathing OR PEEP):ti,ab,kw	9922
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	1694300
#9	MeSH descriptor: [Head Protective Devices] explode all trees	97
#10	(helmet*):ti,ab,kw	459
#11	#9 OR #10	476
#12	#8 AND #11 in Trials	468

EBSCO CINAHL Complete

#	Query	Results
S11	S7 AND S10	26
S10	S8 OR S9	2,980
S9	TI helmet* OR AB helmet*	2,157
S8	(MH "Head Protective Devices")	2,098
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	41,268
S6	TI (continuous positive airway pressure OR CPAP OR nCPAP OR CPPB OR CPPV OR continuous positive pressure ventilation OR CPPV OR airway pressure release ventilation OR APRV OR ((bi-level OR bilevel) N2 positive airway pressure) OR (hyperbaric N1 (respiration OR ventilation)) OR (positive pressure N1 (breathing OR respiration OR ventilation)) OR positive endexpiratory pressure breathing OR PEEP) OR AB (continuous positive airway pressure OR CPAP OR nCPAP OR CPPB OR CPPV OR continuous positive pressure ventilation OR CPPV OR airway pressure release ventilation OR APRV OR ((bi-level OR bilevel) N2 positive airway pressure) OR (hyperbaric N1 (respiration OR ventilation)) OR (positive pressure N1 (breathing OR respiration OR ventilation)) OR positive endexpiratory pressure breathing OR PEEP)	8,111
S5	(MH "Continuous Positive Airway Pressure")	5,335
S4	TI ((lung? OR respiratory OR respiration OR pulmonary OR ventilator?) N2 (depress* OR insufficien* OR fail* OR deficien* OR disturb* OR dysfunction* OR compromis*)) OR AB ((lung? OR respiratory OR respiration OR pulmonary OR ventilator?) N2 (depress* OR insufficien* OR fail* OR deficien* OR disturb* OR dysfunction* OR compromis*)) OR TI (((acute OR adult*) N1 respiratory distress) OR ARDS OR ARDSS) OR AB (((acute OR adult*) N1 respiratory distress) OR ARDS OR ARDSS)	22,824
S3	(MH "Respiratory Failure") OR (MH "Respiratory Distress Syndrome+")	10,890
S2	TX (non-invasive* OR noninvasive*) N3 (oxygen* OR O2 OR ventilat*)	3,999
S1	(MH "Pressure Support Ventilation") OR (MH "Positive Pressure Ventilation+")	11,309

International HTA database (https://database.inahta.org/)
=0 relevant results

"Head Protective Devices"[mhe] OR (helmet*)

LILACS (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F)
=0 relevant results

helmet* [all]

WHO COVID-19 Global literature on coronavirus disease
(https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/)
=40 results

helmet* [all]

Manuscript #2 - Introducing Helmet Non-Invasive Ventilation during COVID-19 pandemic: Early Experience of Two Centres

Introducing Helmet Non-Invasive Ventilation during COVID-19 pandemic: Early Experience of Two Centres

Short Title: Helmet Non-Invasive Ventilation during COVID-19

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Conflict of Interest/Competing Interests

All authors have no conflicts of interest to report. One sample helmet was donated by Intersurgical StarMed (Burlington, Canada) to investigators at the Juravinski Hospital during orientation with the Helmet device.

Author Contributions

DC and BR initially conceived of this study. DC and BR wrote up the study protocol and submitted for ethics approval. DC and RS performed data collection at Juravinski Site and JP performed data collection at the St. Joseph site. DC and RS did the statistical analysis. DC, Deborah Cook, KB and BR wrote up the manuscript. All authors provided edits and feedback.

Implication Statement

This 16 patient case series describes the adoption of helmet non-invasive ventilation in patients with acute respiratory failure of any cause in 2 North American ICUs.

Abstract

Purpose: The helmet is a novel interface for delivering non-invasive ventilation (NIV). We conducted a case series to characterize introduction of the helmet interface in both COVID and non-COVID patients at two-centres.

Methods: We enrolled all patients with respiratory failure admitted to the Juravinski Hospital (Hamilton, Canada) and St Joseph's Health Center (Syracuse, New York) between November 1, 2020 and June 30, 2021 who used the helmet interface (Intersurgical StarMed) as part of this introduction into clinical practice. We collected patient demographics, reason for respiratory failure, NIV settings, device-related complications and outcomes. We report respiratory therapist's initial experiences with the helmet using descriptive results.

Results: We included 16 patients with a mean age of 64.3 ± 10.9 years. The most common etiology for respiratory failure was pneumonia (81.3%). The median duration of NIV during the ICU admission was 67.5 (15.3, 80.8) hours, with a mean maximum IPAP of 13.9 ± 6.6 cm H2O and a mean maximum EPAP of 10.4 ± 5.1 cm H20. Three patients (18.7%) did not tolerate the helmet. Ten (62.5%) patients ultimately required intubation, and 7 (43.4%) patients died while in the ICU. The most common reason for intubation was worsening hypoxia (70%). No adverse events related to the helmet were recorded.

Conclusion: Over the 8-month period of this study, we found that the helmet was well tolerated in over 80% of patients, although, more than half ultimately required intubation. Randomized controlled trials with this device are required to fully assess the efficacy of this interface.

Introduction

Non-invasive positive pressure ventilation (NIV) has been increasingly used as an alternative to endotracheal intubation and subsequent invasive mechanical ventilation[4], especially for those with less severe respiratory disease. NIV has been shown to reduce morbidity and mortality when compared to standard oxygen therapy, and in some cases, invasive mechanical ventilation[4]. This is especially true in patients with chronic obstructive pulmonary disease (COPD), pulmonary edema and more recently in acute hypoxic respiratory failure due to COVID-19[49]. The most recent ERS/ATS guideline strongly recommends NIV for patients who have acute respiratory failure due to chronic obstructive pulmonary disease (COPD) exacerbations or cardiogenic pulmonary edema, and conditionally recommends NIV in patients with acute respiratory failure of a variety of other causes including trauma, post-operative respiratory failure and in patients who are immunocompromised [5].

Typically, NIV is delivered through a face mask interface; however, at higher pressures, the face mask can be difficult to tolerate and can cause significant air leak, thus impairing oxygenation and ventilation[6]. Furthermore, patients using the face mask interface often feel claustrophobic and delirious patients may have difficulty keeping the mask in place; communication and nutrition therapy can also be challenging [7]. The helmet is a relatively new interface used to deliver NIV in patients with respiratory failure. A transparent hood is placed over the entire head of the patient with a seal at the neck using a soft collar. The helmet reduces air leak and improves tolerability due to lack of contact with the patient's face and better seal integrity at the neck[8]. The ability to provide a better seal without obscuring the face also offers other potential advantages including enhanced comfort, and enabling oral intake, and permitting communication. In studies conducted using a breathing patient stimulator, the helmet was found

to be safer in reducing respiratory virus dispersion, compared to facemask NIV or high flow nasal cannula (HFNC), making it particularly effective during pandemic-related illnesses, such as COVID-19, and severe acute respiratory syndrome (SARS) [9, 10].

Small trials in selected populations (ARDS, COVID-19 respiratory failure, community acquired pneumonia) have shown that the helmet is better tolerated, and associated with lower intubation rates, lower mortality, more ventilator free days and shorter ICU length of stay[6, 11, 12, 30]. A recent network meta-analysis of randomized control trials (RCTs) comparing all non-invasive oxygenations strategies in 3804 patients with acute hypoxemic respiratory failure showed lower mortality with helmet NIV when compared to conventional oxygen therapy although this was based on low certainty evidence[13]. We recently performed a systematic review and meta-analysis comparing the helmet and facemask interface for NIV that found the helmet may reduce mortality and intubation in both hypoxic and hypercarbic respiratory failure, although these conclusions were based on low certainty evidence[50].

While the helmet interface has been increasingly used in Europe, especially during the COVID pandemic [15], a lack of large-scale, well designed and adequately powered studies to inform practice on potential risks and benefits has limited its wider adoption. With regulatory approval now across North America, it is possible that helmet NIV could play an important role in the management of acute respiratory failure. Given this, interested ICUs have begun gaining experience with this technology to build familiarity and work towards a pilot randomized clinical trial (RCT) addressing the optimal interface in critically ill patients requiring NIV. The objective of this study was to describe our initial experience using the helmet interface for NIV among patients with acute respiratory failure in 2 tertiary care ICUs. Herein, we report patient

characteristics, reasons for respiratory failure, NIV initiation and settings, device-related complications and patient outcomes.

Methods

Study Design

We enrolled all patients with acute respiratory failure admitted to the Juravinski Hospital ICU in Hamilton, Ontario, Canada and St Joseph's Health Center in Syracuse, New York who were cared for using the helmet interface (Intersurgical StarMed) for delivery of NIV.

We obtained research ethics board approval using a waived consent model and retrospective data collection at both sites (Hamilton Integrated Research Ethics Board # 2021-13066-C, St. Joseph's Health Center Integrate Research Ethics Board # 20-1221-1). We provided training and educational material for helmet initiation and setup to both study sites prior to rollout. Primarily, this was done through multiple orientation sessions with a device representative from Intersurgical Canada and respiratory therapists, physicians and other healthcare professionals who were interested in learning about the new device. One free sample of the helmet device was donated to each centre and the helmet was first tried briefly on a healthy volunteer (in this case, the study author) to build familiarity with the operation of the device. Subsequently, the helmet was then used on actual patients with acute respiratory failure. Further details on exactly how the helmet was set up and used is included in the appendix.

We report findings using the STROBE checklist (Appendix) [51]. We included patients who were 18 years of age or older and were admitted to a critical care unit with either hypoxemic or hypercarbic respiratory failure of any etiology and were treated with NIV through the helmet interface. Patients were admitted between November 1, 2020 and June 30, 2021, which

represents the period between when the helmet was first introduced at both sites and the initiation of a pilot RCT comparing helmet versus facemask interface for NIV delivery in patients with acute respiratory failure at one site (Juravinski Hospital) during the height of the COVID-19 pandemic in Ontario.

Data Collection

We developed and pilot tested a standardized case report form (CRF) for data collection. DC and RS collected data from the medical record in duplicate using medical record numbers (MRNs). Discrepancies were resolved through discussion and/or adjudicated by a third author if necessary. We collected baseline demographic data for all study patients including age, sex, BMI, APACHE II score, comorbidities, reasons for respiratory failure (patients could have more than one reason for respiratory failure) and initial respiratory parameters. For NIV, we collected duration of therapy, the number of episodes of therapy each patient received, the initial NIV settings and the maximum (highest) NIV settings for each patient. We collected positive end-expiratory pressure (PEEP), pressure support above PEEP (PS), fraction of inspired oxygen (FiO2) and tidal volume. We also captured helmet size, and co-interventions such as other non-invasive oxygen support and inotropes/vasopressors. In terms of patient variables, we collected respiratory parameters such as respiratory rate [RR], percentage saturation of O_2 (S_pO_2), PaO_2 (mmHg), and $PaCO_2$ (mmHg) at initiation, 30 minutes after helmet NIV initiation and just before the helmet was discontinued or the patient was intubated. If the helmet was used multiple times in a single patient, we recorded each segment of use as an individual episode. We captured episodes in which the helmet was removed including reasons for removal (e.g., due to

intolerance) and any technical problems with the usage of the helmet noted by the physician or respiratory therapist.

We collected patient outcomes including need for endotracheal intubation (time of intubation and reason for intubation in those requiring intubation), ICU and hospital mortality, ICU and hospital length of stay and adverse events related to helmet therapy. Serious adverse events with the helmet including bradycardia, hypotension, cardiac arrest, vomiting or aspiration were recorded by reviewing respiratory therapist (RT) notes in the patient's medical record during helmet application. Finally, we solicited informal, in-person comments from 5 RTs, including the RT lead, at one site regarding their initial impressions of the helmet device.

Statistical Analysis

We performed descriptive analysis of the patients included in this case series. We summarized data using means with standard deviations, medians with interquartile ranges as appropriate, and counts with percentages. All statistical analysis were performed with Microsoft Excel, version 16.4.3.

Results

Baseline Demographics

We included 16 eligible patients (13 from the Hamilton site and 3 from the Syracuse site). Of these, 5 (34.4%) were female and the mean (standard deviation) age was 64.3 ± 10.9 years (Table 1). The mean APACHE II score was 9.7 ± 4.9. Patients were placed on helmet NIV an average of 68.6 ± 56.7 hours from the time of hospital admission. The most common patient comorbidities included smoking (37.5%), COPD (31.3%), cancer (31.3%) and diabetes mellitus

type 2 (31.3%) (Table 1). The most common causes of respiratory failure were pneumonia (81.3%), COVID-19 (62.5%) and ARDS (50%) (Table 1). One patient was on vasopressors when helmet NIV was initiated.

NIV Initiation and Settings

Within a month of our initial training sessions, helmet utilization commenced at both sites. Figure 1 illustrates a patient's possible clinical trajectory when the helmet was used. Eight (50%) of the included patients were initially treated with HFNC before being placed on helmet NIV, with the remainder being trialed on either nasal prongs (NP) (4 patients) or non-rebreather mask (NRB) (2 patients) prior to helmet initiation. Of note, one patient was extubated directly to helmet NIV, and one patient was initially started on facemask NIV before being switched to helmet NIV.

The median (IQR) duration of helmet NIV was 67.5 (15.3, 80.8) hours with the mean initial PEEP being set at 8.4 ± 2.4 cm H2O and the mean initial pressure support (PS) being set at 12.9 ± 4.1 cm H2O (Table 2). The mean maximum PEEP was 10.4 ± 5.1 cm H20 with the mean maximum PS being 13.9 ± 6.6 cm H2O. The initial mean FiO2 settings were 56.6% ± 23.4%. Heat and moisture exchanges (HME) were used to humidify the inhaled air for all patients. The trigger threshold for all patients were set to be as sensitive as possible without allowing for auto-triggering.

Outcomes

Table 3 outlines patient outcomes. Of those treated with helmet, 10/16 (62.5%) patients were ultimately intubated. The primary reason for intubation was hypoxia (70%). In those that required intubation, patients received helmet NIV for a median (IQR) of 42.0 (5.5, 72.0) hours before intubation. Three (18.7%) patients did not tolerate helmet NIV due to increased agitation and were switched to facemask NIV (n=2) or HFNC (n=1). All 3 of these patients had COVID ARDS and were subsequently intubated after failing this alternative non-invasive oxygen support. Of those enrolled, 7/16 (43.4%) patients died in ICU, and 9/16 (56.3%) died in hospital. The mean duration of stay for all patients in the ICU was 30.1 ± 28.4 days and the mean duration of hospital stay was 36.1 ± 29.9 days. There were no serious adverse events reported with the helmet.

RT Impressions

Common concerns amongst the RTs regarding helmet use as recorded from their informal comments were primarily regarding oral dryness, along with skin breakdown and discomfort at the armpits.

Discussion

Helmet NIV was generally well tolerated by patients and well adopted by healthcare staff. While over half of the patients treated with helmet NIV were ultimately intubated, primarily because of hypoxia, there were no significant adverse events recorded with helmet use. Overall, the helmet appears to be a viable and feasible alternative to facemask NIV, although large randomized trials examining this interface are necessary to better elucidate the benefits, risk, and comfort in critically ill patients with respiratory failure.

Most included patients were able to tolerate long periods of continuous NIV using the helmet device without significant adverse events. While 3 patients were unable to tolerate the helmet and were switched to alternative respiratory support devices, it is important to note that all 3 patients were subsequently intubated. Thus, it is uncertain whether the patients did not tolerate the helmet itself, or whether they would have required intubation regardless of modality of non-invasive respiratory support. Commonly described complications of the NIV including ventilation associated pneumonia (VAP), and gastric distension or emesis [52] were not observed within our series, although this may have been related to careful selection of patients or a reflection of the small numbers enrolled. In addition, despite the increased dead space associated with the helmet, ventilator settings were well within normal NIV settings and did not cause any issues with carbon dioxide recirculation, such as hypercarbia and respiratory acidosis. Finally, while the majority of included patients had hypoxic respiratory failure, it is important to note that the helmet was also used in 3 patients with hypercarbic respiratory failure secondary to COPD exacerbation or drug overdose.

More than half of the patients included in our case series were eventually intubated and almost half of them died. A recent observational study including a similar patient population (hypoxic respiratory failure) who required facemask NIV showed a similar intubation rate of 54% but a much lower mortality rate [53]. Moreover, a systematic review and meta-analysis that compared helmet NIV to facemask NIV showed lower rates of intubation and mortality as compared to this case series of patients, indicating a less sick population than this current study [52]. Therefore, whether the findings from this case series are generalizable to a less hypoxemic population

remains uncertain. We believe there are a few explanations for the high illness severity in this study population. First, in both study centers, patients with hypoxic respiratory failure are typically initiated on HFNC if standard oxygen therapy fails, as was seen in over 50% of our study patients. Therefore, patients initiated on helmet NIV had already failed one type of non-invasive oxygen support (e.g., HFNC), suggesting they were sicker than the populations examined in most NIV studies. Second, a majority of study patients had respiratory failure due to COVID-19 and were enrolled during the height of the COVID-19 pandemic. Patients with respiratory failure due to COVID-19 may have worse outcomes as compared to those without COVID-19 [54] and lack of resources, along with increased healthcare burden may have also contributed to poor outcomes in this population.

Ideally, the introduction of a new technology in the critical care setting requires a full health technology assessment beyond just clinical effectiveness before being implemented into clinical practice. While beyond the scope of this study, it is important to assess the cost effectiveness of this technology when compared to face mask and other non-invasive modes of respiratory support, such as HFNC. From personal experience, the cost of the helmet is more than the facemask interface ($ 200 CAD vs. $ 50 CAD), however, to our knowledge, a more robust cost effectiveness or cost utility study, using analytic models and direct comparisons do not exist. Other than clinical effectiveness and cost-effectiveness, we do not foresee any ethical, legal or social considerations that would impede broader implementation of the helmet in the critical care space after the initial training and uptake period that is required when adopting any new technology. The helmet technology is similar to the already used facemask NIV, using similar ventilators and titrated to similar patient outcomes.

Strengths of this study include a pragmatic design where clinicians were encouraged to apply the helmet in patients who they considered to appropriate and to titrate as they thought appropriate, with a protocol being available only as guidance. Since the purpose of this study was to not just describe our experience with a new technology but also build competence and comfort with it, this ensured that both these objectives were met. Previous studies with the helmet, both randomized and observational, included patients with specific aetiologies of respiratory failure, limiting the external validity of the use of helmet interface for NIV. This study included patients with several types of acute respiratory failure, including one patient with a toxic overdose, which has never been described before. Moreover, while informally obtained, we are the first to collect and report respiratory therapist feedback on the helmet utilization. Finally, despite the challenges of incorporating a new respiratory support technology in a healthcare setting during a viral respiratory pandemic, the underlying etiology of respiratory failure was uniquely COVID-19 hypoxic respiratory failure in 62.5% of patients.

Our study has important limitations. First, given that this was a case series, no inferences regarding causation or efficacy or harm can be made. Given that clinicians chose which patients were cared for using the helmet interface, selection bias was a serious concern. The small number of patients is another limitation. While we sought informal feedback respiratory therapists, we did not conduct structured interviews on RTs or solicit the impressions of physicians, nurses or patients.

Conclusion

This case series describes experience with the helmet NIV interface in critically ill patients with respiratory failure in 2 centers. We found that the helmet was reasonably well tolerated in a majority of patients, although most patients using the helmet ultimately required intubation. This technology requires more research before it is used widely. Observational studies would be useful to better characterize helmet tolerance and safety in a larger sample size of patients. Qualitative studies examining issues with helmet use among clinicians and patient experience with the helmet compared to the facemask would also be valuable in evaluating this new technology. Randomized control trials comparing helmet to facemask NIV, or to other non-invasive respiratory support devices, such as HFNC are needed to determine the efficacy of this device. Given the increased cost of the helmet compared to the facemask NIV, a cost-effectiveness or cost utility study would be important before this device is commonly adapted in critical care settings everywhere.

Table 1: Baseline Demographics of Included Patients

Characteristic	All Patients
Demographic	
Average Age	64.3 ± 10.9
# of Male (%)	11 (68.8)
# of Female (%)	5 (31.3)
Average APACHE II Score	9.7 ± 4.9
Time to NIV from admission (hours)	68.6 ± 56.7
Medical History	
Cardiovascular Disease (%)	3 (18.8)
Asthma (%)	2 (12.5)
COPD (%)	5 (31.3)
T2DM (%)	5 (31.3)
Smoker (%)	6 (37.5)
Cancer (%)	5 (31.3)
Immunocompromised (%)	2 (12.5)
Etiology of Respiratory Failure	
Pneumonia (%)	13 (81.3)
ARDS (%)	8 (50.0)
Pulmonary Edema (%)	1 (6.3)
Aspiration (%)	1 (6.3)
Postoperative (%)	0 (0)
Pulmonary Embolism (%)	0 (0)
Toxic (%)	1 (6.3)
Neuromuscular Disease (%)	0 (0)
AECOPD (%)	2 (12.5)
COVID-19 (%)	10 (62.5)

Mean (Standard Deviation) for continuous variables. NIV – Non-invasive ventilation, COPD - Chronic Obstructive Pulmonary Disease, T2DM - Type 2 Diabetes Mellitus, ARDS – acute respiratory distress syndrome, AECOPD – COPD exacerbation

Table 2: Average NIV Parameters

Average Duration (hours) (mean ± SD)	74.1 ± 81.9
(median, IQR)	67.5 (15.3, 80.8)
Average Initial PEEP (cm H20)	8.4 ± 2.4
Average Initial $P_{Support}$ (cm H20)	12.9 ± 4.1
Average Maximum PEEP (cm H20)	10.4 ± 5.1
Average Maximum $P_{Support}$ (cm H20)	13.9 ± 6.6

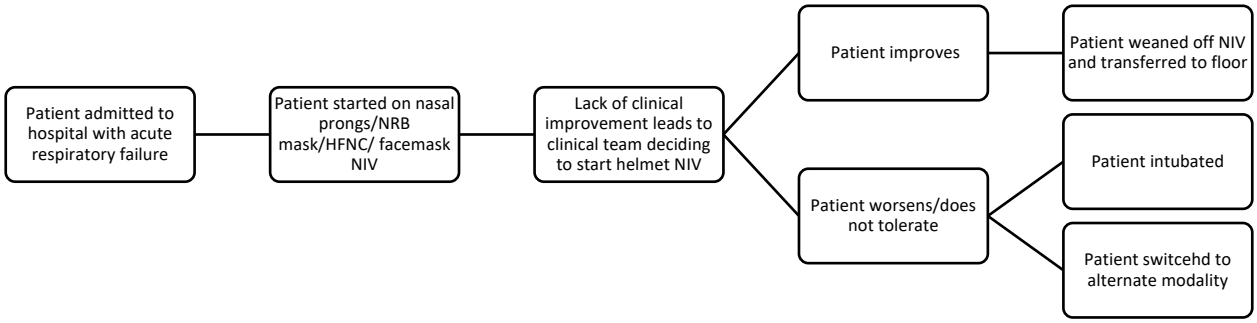
Results in Mean (Standard Deviation), unless otherwise stated. IQR = interquartile range. cm H20 = centimetres of water, PEEP = positive end expiratory pressure, $P_{support}$ = Pressure support

Table 3: Patient Outcomes

# of Intubations (%)	10 (62.5)
# ICU Mortality (%)	7 (43.4)
# Hospital Mortality (%)	9 (56.3)
Average LOS in ICU (days)	30.1 ± 28.4
Average LOS in Hospital (days)	36.1 ± 29.9
Etiology of Intubation	
Hypoxia (%)	7 (43.4)
Neurologic Failure (%)	1 (6.3)
Respiratory Failure (%)	1 (6.3)
Circulatory Failure (%)	1 (6.3)

Results in Mean (Standard Deviation) for continuous variables. ICU = intensive care unit, LOS = length of stay.

Figure 1: Clinical Trajectory During Helmet Use



Appendix

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants8	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

StarMed NIV Helmet Usage

- Single patient use (for up to 7 days)
- Must be used with **dual limb** vent circuit
    - **Servo-i**
        - Connect inspiratory limb to one port and expiratory limb to opposite port
            - Ports are interchangeable (doesn't matter which limb goes to which port)
    - **Hamilton G5**
        - Flow sensor, patient wye, and dual limb circuit to one port & cap off opposite port
            - Use blue cap from heated circuit to block opposite port
    - **Do not** use StarMed helmet with the **V60**
- Only use helmet with a **dry circuit** – heated humidity will cause excessive buildup of condensation
- Smooth bore tubing recommended for noise reduction (but can use standard circuits vent circuits)
- Place a special **low resistance filter** at the inspiratory port of the helmet for noise reduction
    - A standard filter will create too much resistance
- Determine appropriate helmet size by using supplied measuring tape around patient's neck to measure neck circumference
- Requires 2 people to place helmet on patient's head
    - Open large access port & check one-way valve
    - Pull back film/seal on either side when placing over head
    - Secure straps snuggly under patient's arms
        - Adjust length of straps so that rigid ring is about 1 cm from patient's shoulders
    - Use bulb from art line pressure bag to inflate inner neck cushion for comfort
    - Close large access port & start vent to inflate/pressurize helmet
- **NIV mode** is recommended
    - Consider **invasive PSV** to access/adjust additional parameters if needed (ie: trigger, ramp, etc)
- Must set **minimum parameters** to ensure **CO2 clearance**:
    - **PEEP 5 cmH20 (minimum)**
    - **PS 12 cmH2O (minimum)**
    - Some pressure will be lost to the helmet – may need to set parameters higher than expected
        - Consider setting PEEP & PS **30%-50% higher** than you usually would
- Set **trigger** as **sensitive** as possible (without inducing auto triggering)
- Set **ramp/slope** as **fast** as possible (titrate to patient comfort)

- Displayed **volumes** will be inaccurate
    - Vt will be much larger than normal because helmet is considered the "lung"
        - 50%-75% of the Vt delivered is distributed to the helmet
    - You can trend the Vt but do not assume this is what the patient's lungs are receiving
- Adjust alarm limits appropriately
- ETCO2 monitoring
    - Cuvette can be placed at expiratory outlet of the helmet
    - Consider measuring ETCO2 inside the helmet using ETCO2 nasal cannula

Manuscript # 3 - Helmet Non-Invasive Ventilation versus Facemask Non-Invasive Ventilation in Acute Respiratory Failure: A Pilot Randomized Control Trial

Helmet Non-Invasive Ventilation versus Facemask Non-Invasive Ventilation in Acute Respiratory Failure: A Pilot Randomized Control Trial

Dipayan Chaudhuri

Introduction: Helmet non-invasive ventilation (NIV) is a new modality of NIV that replaces the traditional face-mask interface with a transparent hood with a seal at the neck. While smaller studies have indicated that the helmet may be superior to the facemask in specific causes of acute respiratory failure, such as ARDS or COVID-19 related respiratory failure, the overall certainty of evidence is low. Thus, we hoped to conduct a pilot randomized control trial examining the feasibility of performing a large trial comparing helmet NIV to facemask NIV in patients with acute respiratory failure.

Methods: This is an ongoing single centre, pragmatic, unblinded, concealed allocation, parallel-group, pilot RCT conducted in the medical surgical ICU at Juravinski Hospital in Hamilton, Ontario, Canada. The goal sample size is 50 patients. Adult patients admitted to the ICU with acute respiratory failure and deemed to require NIV are randomized to either helmet or facemask modalities. The primary feasibility outcomes are study recruitment rate and protocol adherence rate. Clinical outcomes that will be important for the full trial including endotracheal intubation, mortality, length of stay, duration of NIV, duration of IMV, adverse events and comfort are also collected.

Results: Since we began enrollment in November 2021, we have screened 22 patients and 7 have been enrolled. Of these, 4 have been randomized to the helmet arm and 3 to the facemask arm. With 7 enrollments over 6 months (1.2 patients/month), so far we have met our goal recruitment rate of one patients per centre per month. Protocol adherence has also met its goal rate of 6/7 (86%). However, there have been 3 crossovers in the 7 included patients.

Conclusion: In this ongoing pilot feasibility trial, feasibility goals have been met so far. However, a high rate of crossover and slowdown in recruitment during the height of the COVID-19 pandemic have presented challenges to ongoing conduct of the study. Enrolling more

sites in the study, adding incentives for healthcare workers to enroll patients and improving site education are all techniques that are being applied going forward to tackle these challenges.

Helmet non-invasive ventilation (NIV) represents a relatively novel method for delivery of NIV for patients with acute respiratory failure (ARF). Compared to the traditional facemask interface, the helmet is a transparent hood that is placed over the entire head of the patient. Helmet NIV uses a soft collar to seal the hood at the neck. Physiologic studies, including randomized controlled trials (RCTs) suggest that the helmet, compared to a facemask, reduces inspiratory effort and air leak, preserves lung volumes, and is better tolerated [1–3]. Providing a seal without obscuring the face maintains a patient's ability to communicate and enables oral intake. Compared to facemask, the helmet also enables a superior seal rendering it valuable in the context of infectious respiratory diseases [4]. A recent systematic review including 949 patients from 16 RCTs, found that helmet NIV may reduce mortality and intubation, compared to facemask, in patients with ARF of diverse etiologies. [5]. However, these findings were based on low certainty evidence mostly due to imprecision as all included studies were small (the largest of which enrolled only 188 patients). Furthermore, helmet technology has evolved significantly since these initial RCTs were published and has been modified to reduce air leak and enhance patient comfort. Thus, large scale, well-designed and adequately powered RCTs are needed to assess the net clinical benefits associated with helmet NIV vs bilevel NIV on clinically important outcomes.

Previous studies have examined helmet NIV for specific etiologies of ARF [2, 6–9]. We hypothesize that helmet NIV has utility as compared to facemask for all causes of ARF. Results from our systematic review support this, showing that helmet NIV may be superior to the facemask in both hypoxic and hypercapnic respiratory failure[5]; however, these findings were limited by low certainty. Prior to embarking on a large scale RCT, it is important to determine.

Assessing feasibility provides opportunity to streamline research protocols and operating procedures prior to launching large studies; affirming or refuting feasibility helps to ensure efficient use of research funding for subsequent studies.This is especially true for this topic, given that helmet NIV represents new technology applied in a fast-paced acute care setting with significant time pressures and constraints.

The objective of this pilot trial is to **test the feasibility** of conducting a large RCT addressing the following research question: In adult patients admitted to the intensive care unit (ICU) with ARF of any etiology (hypoxemic, hypercapneic or both) and who require NIV, is there any difference between the helmet interface as compared to the facemask interface with regard to need for invasive mechanical ventilation or mortality?

Methods

This is an ongoing single centre, pragmatic, concealed allocation, unblinded, parallel-group, pilot RCT conducted in the medical surgical ICU at Juravinski Hospital in Hamilton, Ontario, Canada. This study was approved by the Hamilton Research Ethics Board (HiREB # 2022-13412-AP). The primary and secondary outcomes of this feasibility trial reflect feasibility metrics. The study protocol was registered on clinicaltrials.gov (NCT05022173). We report out findings using the CONSORT statement (Appendix).

We will screen all patients admitted to the ICU during daytime hours (9 am to 5 pm) during regular business days. To be eligible for this trial, patients must be enrolled within an hour of NIV initiation in the ICU. Given the urgency of treating patients with ARF, there is a need to enrol patients as soon as possible to properly evaluate the intervention while avoiding upfront contamination. At this time, concerns may exist regarding patient's capacity to participate in research decision-making [10], consequently a hybrid consent model is being used

for this trial, as approved by the REB. With this consent model, if the patient is able to engage in a consent encounter at the time of eligibility or if the substitute decision maker (SDM) is immediately available, they will be directly approached for consent. However, if the patient is not able to engage in a consent encounter and the SDM is unavailable, a deferred consent model will be utilized. If deferred consent is used, the patient or SDM will be approached as soon as possible after randomization for consent. If the patient or the SDM subsequently decline further participation, then further trial interventions will be halted. If a patient or SDM declines participation, we will confirm whether the data that were collected to that point can be used. If not, the randomization will be recorded and patient will be represented in the CONSORT diagram incorporating all data permitted as per ethics review.

Study Population

In keeping with the pragmatic approach and to ensure generalizability and applicability of results, we developed broad inclusion criteria. We include patients who are: 1) admitted to the adult ICU and 2) deemed to require NIV, as per the clinical team, for ARF of any etiology. Patients who have already been started on bilevel NIV (for example in the emergency department) are eligible for the study as long as they received bilevel NIV for less than an hour inside the ICU.

We will exclude patients with: 1) impending cardiac arrest or need for intubation, 2) Glasgow coma scale <8, 3) tracheostomy or upper airway obstruction, 4) elevated intracranial pressure, 5) untreated pneumothorax, 6) advanced directives that state endotracheal intubation is not part of their goals of care (do not intubate order documented), and those who 7) have facial trauma, 8) are unable to wear the helmet or facemask, and 9) regularly use NIV chronically or

nocturnally. Co-enrollment into other trials and studies is permitted, where feasible, to be determined on a study-by-study basis as agreed upon by relevant steering committees.

Site Preparation

Prior to site activation, the study centre and respiratory therapists (RTs) were educated on helmet NIV use and trouble-shooting with a representative of the manufacturer. In addition, we performed a run-in observational period in which helmet NIV was used in clinical practice for approximately 6 months prior to enrolling patients to build experience with the device before the trial began.

Experimental and Control Interventions

Patients are being randomized in a 1:1 manner with allocation concealed using undisclosed variable block sizes of 2, 4, or 6 through a centralized computer system. Randomization used www.randomize.net.

Patients randomized to the intervention arm receive helmet NIV through a phthalate free helmet (CaStar, STARMED) via an ICU ventilator (regular ventilator or NIV-specific ventilator compatible with the CaStar helmet). This model of the helmet is one of two that are approved in Canada, and the only one that is currently available for mass purchase. It is also the most common helmet NIV device used for clinical research.

A single helmet can only be used for one patient for up to 7 days. (See Appendix 1: Helmet NIV set up). Each participant has his/her neck circumference measured to determine appropriate helmet size. The helmet is secured by padded armpit braces connected to a neck seal, to create a closed circuit. As per the helmet manufacturers, the minimum positive end-expiratory

pressure (PEEP) is set to 10 cm H20 and the minimum positive pressure support (PS) to 12 cm H20 to maximize helmet stiffness. PEEP is titrated in 2 – 3 cm H20 increments at the discretion of the RTs to keep SPO2 >90% (or >88% for patients with chronic obstructive pulmonary disease (COPD) with an FiO2 <50%. PS is titrated up in increments of 2 -3 cm H20 to maintain a respiratory rate less than 25/min and limit accessory muscle use. RTs adjust PS and PEEP settings to ensure patient comfort, at their discretion. The inspiratory trigger is set as sensitive as possible without inducing auto-triggering and the ramp/slope is set as high as possible, titrated to patient comfort. To prevent carbon dioxide (CO2) rebreathing and monitor CO2 levels, a CO2 monitor can be placed at the Y-of the expiratory limbs. Patients may receive high flow nasal cannula (HFNC) or any other non-invasive respiratory support device in between NIV sessions or off NIV, as clinically indicated and as per the decision of the bedside clinician

Weaning is initiated once patients are stable on current helmet NIV settings for at least 2 hours at the discretion of bedside clinicians. Helmet NIV is discontinued when PS and PEEP are both less than 10cm H20 with an FiO2 <50%, no accessory muscle use, RR <25/min, SpO2 >90% and the patient is comfortable. If a patient fails weaning and requires re-initiation of helmet NIV, the helmet may be reapplied and the above process is repeated as needed, or until the patient is intubated. If needed, supplemental airflow or HFNC may be added through the access port on the helmet. In addition, the access port can be used to deliver oral medications and sips of water. For nutritional intake, a nasogastric tube (NG tube) can be inserted through one of the sealed catheter ports. Nebulized medications can be delivered through the access port without interruption of NIV.

Failure of NIV therapy and the decision to intubate in both arms is based on criteria similar to previous NIV studies [6]. The decision to intubate is made by the primary care team

taking care of the patient using these criteria as a guide. Clinicians may consider intubating patients in the case of any one of: 1) neurological deterioration/failure to protect airway, 2) worsening respiratory failure (SpO2 <88%, RR >36/min), 3)helmet/facemask intolerance, 4) airway bleeding or 5) unmanageable secretions. Other management is at the discretion of the treating clinical team.

Patients in the control arm are randomized to the traditional oronosal interface with application of bilevel NIV. The facemask group use the same ICU ventilator (or NIV-specific ventilator) being used for the helmet NIV group. The minimum positive PEEP is set to 5 cm H20 and the minimum positive PS to 0 cm H20. As with the helmet, PEEP is titrated in 2 – 3 cm H20 increments to keep SPO2 >90% (or >88% for patients with COPD) with a FiO2 <50% as per the discretion of the RT. PS is titrated up in increments of 2 – 3 cm H20 to obtain a RR<25/min and with a goal to limit accessory muscle use. RTs may also make changes to either PS or PEEP settings to adjust for comfort, at their discretion. The inspiratory trigger and ramp slope is titrated to patient comfort. As with the helmet NIV arm, patients may receive HFNC or any other non-invasive respiratory support device between NIV sessions or off NIV. Failure of bilevel NIV therapy, decision to intubate and weaning is based on identical criteria to that of the intervention group. Bilevel NIV is discontinued when with gradual downward titration both PS and PEEP are less than 5 with FiO2 <50%, with no accessory muscle use, RR <25/min, SpO2 >90% and the patient is comfortable. As per the helmet NIV arm, if a patient fails weaning and requires re-initiation of bilevel NIV, the facemask may be reapplied and the above process repeated as needed, or until the patient is intubated. Other management is at the discretion of the treating team.

Blinding

Given the nature of the intervention and the control (helmet NIV and bilevel NIV), it is not possible to blind treating clinicians (physicians, nurses, RTs), research coordinators or investigators to treatment allocation. However, the statistician is blinded to treatment allocation. Group allocation is stored on a secure online case report form (CRF) that is password protected. Although the primary outcome of intubation is based on suggested predefined criteria, the threshold to intubate is subject to bias due to lack of blinding. To monitor for this, reasons for intubation and pre-intubation vitals for all patients who are intubated are being recorded, as well as adherence to suggested criteria for intubation.

Primary Feasibility Outcome

Recruitment Rate: A successful recruitment rate is defined as one patient randomized per centre per month. We will capture all excluded and eligible non-randomized patients. We will review screening logs to determine whether any modifications to the eligibility criteria may be needed. We will assess barriers to enrolment and examine avenues for improvement, if necessary.

Secondary Feasibility Outcome

Protocol Adherence: Successful protocol adherence will be defined as at least 75% of patients receiving at least 4 hours of NIV delivered with the appropriate interface in the first 24 hours of randomization. We chose this threshold as we believed that 4 hours was a reasonable amount of time for a trial of helmet NIV to allow RT-assisted patient adaptation to the interface. Patients whose exposure to the intervention were less than 4 hours will be included in the final

analysis. All protocol violations are reviewed with the steering committee and if adherence is low, the principal investigator (PI) and research coordinator will meet to discuss strategies to improve this.

Crossovers from helmet NIV to bilevel NIV or vice versa are also being measured and recorded. We will aim for a crossover rate of less than 10%. Patients who are switched from helmet or bilevel NIV to HFNC or other non-invasive oxygen modalities due to intolerance are not included in the crossover count. Reasons for cross-over are currently listed in freeform, with the goal of developing a taxonomy of reasons for the larger study.

Consent Encounter Outcome

Data on consent (e.g., individuals involved in the consent encounter, outcome of the consent encounter) are also being collected but not considered a formal feasibility outcome.

Clinical Outcomes

In the larger trial, we will aim to determine whether the use of helmet NIV as compared to bilevel NIV impacts on patient-important outcomes. Outcomes for the full trial will include: endotracheal intubation (using predefined criteria as a guide for when to intubate), ICU mortality, hospital mortality, ICU length of stay, hospital length of stay, duration of NIV (total duration and daily duration), duration of invasive mechanical ventilation (IMV), adverse events and comfort. Although these outcomes are captured in this pilot trial, the numbers are too small to make any inferences about the comparative effects.

Data Collection

Using a CRF that is later transcribed into an electronic CRF (http://www.project-redcap.org) that is encrypted and password-protected, research staff collect data on all enrolled patients during their ICU stay and up to 28 days post randomization. All CRFs were pre-tested and edited for clarity before trial initiation. Collected data includes 1) baseline data (site randomized, age, gender, BMI, APACHE II score, time from hospitalization to randomization, past medical history, cause of acute respiratory failure, initial respiratory parameters); NIV parameters per NIV trial (helmet NIV vs bilevel NIV, total duration of NIV, initial NIV settings, highest NIV settings, respiratory parameters 30 minutes after placing helmet on, respiratory parameters before taking helmet off, removal of the helmet due to intolerance); and outcomes as stated earlier. All electronic CRFs are encrypted and password protected. Paper CRFs are stored in a locked room and file cabinet at the local site.

Statistical Analysis

We calculated the feasibility sample size using a 95% CI approach examining the feasibility outcome of protocol adherence. The feasibility threshold (75%) and an expected adherence rate (95%) were determined a priori. If the observed adherence rate is 95%, we will be able to exclude 75% adherence or lower, with a power of 80% using a sample size of at least 47 patients. To be conservative, we planned for 50 patients (25 per study arm). This sample size will allow us to assess both *a priori* feasibility outcomes in a cost-effective manner.

Given that patients are being enrolled in this pilot trial at the time of this report, descriptive analyses of those included to date are presented. Clinical data were analyzed as a

total cohort of enrolled patients, rather than in 2 treatment groups. We summarized data using mean and standard deviations, or median and interquartile range, where appropriate, and counts with percentages. All statistical analysis were performed with Microsoft Excel, version 16.4.3.

Study Data and Safety Monitoring

An SAE is defined as any unfavourable or unintended sign, symptom or disease that was associated with either intervention and that resulted in death, a life threatening event, prolonging of existing hospitalization or persistent/significant incapacity. The research coordinator reviews the patient chart daily for any adverse events during data collection. Also, bedside clinicians are encouraged to report any adverse events to the research coordinator or the PI. SAEs are collected through a standardized study case report form (Appendix) and a decision is made on whether to continue enrollment or suspend enrollment, pending further review by the Steering Committee. The Steering Committee consists of the PI, along with the PI's research supervisor and the trial research coordinator. The Steering Committee reviews each serious adverse event (SAE) and pledges to submit reports as relevant to the relevant REB(s).

An independent data safety and monitoring board (DSMB) will be established before the start of the larger trial and will include a biostatistician, national and international experts in critical care medicine, and experts in clinical trials. A DSMB will not be convened for the pilot trial but will review the data from the pilot trial if patients from it are rolled forward into the larger trial.

Results

From November 2021 to May 2022, we have screened 22 patients and 7 patients were enrolled (Figure 1). Of these, 4 patients were randomized to helmet NIV and 3 patients were bilevel NIV arm. Table 1 describes the baseline characteristics of included patients which are comparable between groups. Table 2 describes the mean NIV settings between groups.

At this point of the pilot, data collection was complete for 5 out of 7 patients. For the last 2 patients, 28 day follow up is not yet complete as they were enrolled less than a month ago. Data from all 7 patients were included when possible. The total duration of non-invasive ventilation was 9.63 hours (median, interquartile range [IQR]: 4.56 to 15.10 hours). Of the 7 included patients, 3 (42.9%) were intubated, 2 due to hypoxia and 1 due to high respiratory rate and fatigue. Of the 5 patients for whom data collection has been completed, 4 (80%) have died, three (60%) in ICU and one in hospital (20%). The average length of ICU stay of all included patients (including the 2 for whom data is still being collected) is 4 days (median, IQR: 2.5 to 18 days) and the median hospital stay is 17 days (IQR: 8.5 to 30 days). There were no serious adverse events recorded.

Feasibility Outcomes

1. Recruitment - With 7 enrollments over 6 months (1.2 patients/month), so far we have met our goal recruitment rate of one patients per centre per month.
2. Protocol adherence – At this time, protocol adherence is 6/7 (86%) as all patients except for one tolerated NIV for at least 4 hours in the first 24 hours of randomization. This patient was switched from helmet NIV to bilevel NIV in the first 24 hours as he/she required

plasmapheresis and the armpit straps of the helmet were prohibitive to plasmapheresis flow. Additionally, 2/7 patients (28%) crossed over – one from bilevel NIV to helmet NIV due to nasal bridge breakdown on study day 22 and one from helmet NIV to bilevel NIV due to claustrophobia on study day 3.

Evaluation of Feasibility

While we met our initial feasibility outcome so far, only 7 patients contributed to this assessment in a single center. A 4-year enrollment period as projected with this enrolment rate is protracted for a 50 patient single centre, pilot trial. Enrollment would need to be increased to assure feasibility for a larger study.

We reflected on measures that could be carried out to enhance feasibility. First, the recruitment rate could be increased to target 2 patients per centre per month. We found that this may be a realistic goal as recruitment rates in the months of December, January and February were quite low due to the increased healthcare demands, healthcare worker sick leave and burnout secondary to the impact of COVID at our centre during this time. Since abatement of this wave, enrollment has increased almost three-fold. Finally, we hope to expand to a second centre in the coming months as a multicentre pilot trial is required to authentically assess the feasibility of a larger multicentre trial.

Discussion

This pilot trial was designed to assess whether it would be possible to conduct a large multicentre RCT comparing helmet and bilevel NIV in patients with ARF. While still ongoing, early results are encouraging and suggest feasibility with some hesitations. With expansion to a

second site and decreased COVID-related healthcare burdens, an expanded phase of this pilot trial will generate more realistic information on feasibility of this protocol.

The primary outcomes of this RCT were to examine whether it was possible to achieve a high enough recruitment rate and protocol adherence to conduct a larger multicentre trial. A previous RCT [6] aiming for a 20% absolute reduction in the primary outcome of intubation calculated a required sample size of around 200. Our systematic review [5] estimated a 16.5% absolute reduction rate in intubation when comparing helmet NIV to bilevel NIV, and thus, using these estimates, we calculated that a full RCT would require more than 300 patients to detect a clinically important difference between helmet NIV and bilevel NIV. Based on our current recruitment rate, we estimate that we could enroll all patients for such a trial in about 2 to 3 years if we were to enroll at 8-10 study centres. Further, given that this trial required adoption of a new technology and its use in a critically ill population, it is vital to assess the ability for a centre to be able to adhere to the trial protocol. To succeed in this endeavour, we included a run-in period to build experience and comfort of the multidisciplinary personnel engaged with helmet NIV use before enrolling patients in the trial. Our experiences so far have really underscored the value of this approach and was an important lesson that we will use in other sites going forward.

One of the key challenges we have encountered so far is a high crossover rate due to a variety of reasons including patient comfort and technical issues. While a small amount of crossover is likely impossible to prevent in a trial of this design, there are a few strategies we can undertake to mitigate this. First, we will endeavour to educate the trial centres in the importance of preventing cross-over in order to properly address the research question. This would include

highlighting that helmet NIV and bilevel NIV are separate treatment arms, with patients being randomized to one arm or the other. Second, we will request that if a patient requests to be switched from one form of NIV to the other, or a bedside clinician advocates a switch, a discussion is held with the physician-on-call and if possible, the local PI, to understand the rationale, honour it, but ensure that the crossover is absolutely necessary. Finally, while we will perform primary intention-to-treat analysis for the larger study, we will also conduct a per-protocol analysis.

Another challenge in conducting this pilot trial has been the reduced recruitment rate that occurred in the late winter months. Monthly reviews of trial enrollment numbers between the research coordinator and the PI were essential to quickly identify that the increased healthcare pressures from the COVID-19 pandemic were partly responsible. While the modifications we made to improve recruitment have so far proven to be helpful, it is important to acknowledge that the current protocol is vulnerable if another wave of COVID-19 threatens to overcome the healthcare system. While this may be impossible to avoid when conducting a trial of a novel technology that requires considerable healthcare worker education and buy-in, nonetheless, it is an important issue to be aware of and plan for moving forward.

Finally, the difficulties involved in implementing a new technology in a dynamic field like critical care cannot be understated. Obtaining institutional approval, educating healthcare workers, creating buy-in and eliciting feedback are all critical aspects that must be carefully undertaken before a trial can be started. In this case, this had to be done in a pandemic setting the likes of which had never been faced in our Canadian healthcare system. The lessons learned

therein illustrate the importance of ensuring that such a project cannot be conducted without full institutional support and careful, thorough implementation with frequent reassessments and opportunities for feedback. Most importantly, without full support of all healthcare professionals who are involved in providing care related to the device, the feasibility of the trial is threatened.

Pilot randomized control trials are critical to assess the feasibility of implementing larger RCTs, especially when using complex trial designs and in acute healthcare settings[11]. In our ongoing pilot randomized control trial, issues regarding slow enrollment and high crossover rates represent important feasibility challenges that need to be addressed to evaluate feasibility of a larger trial.

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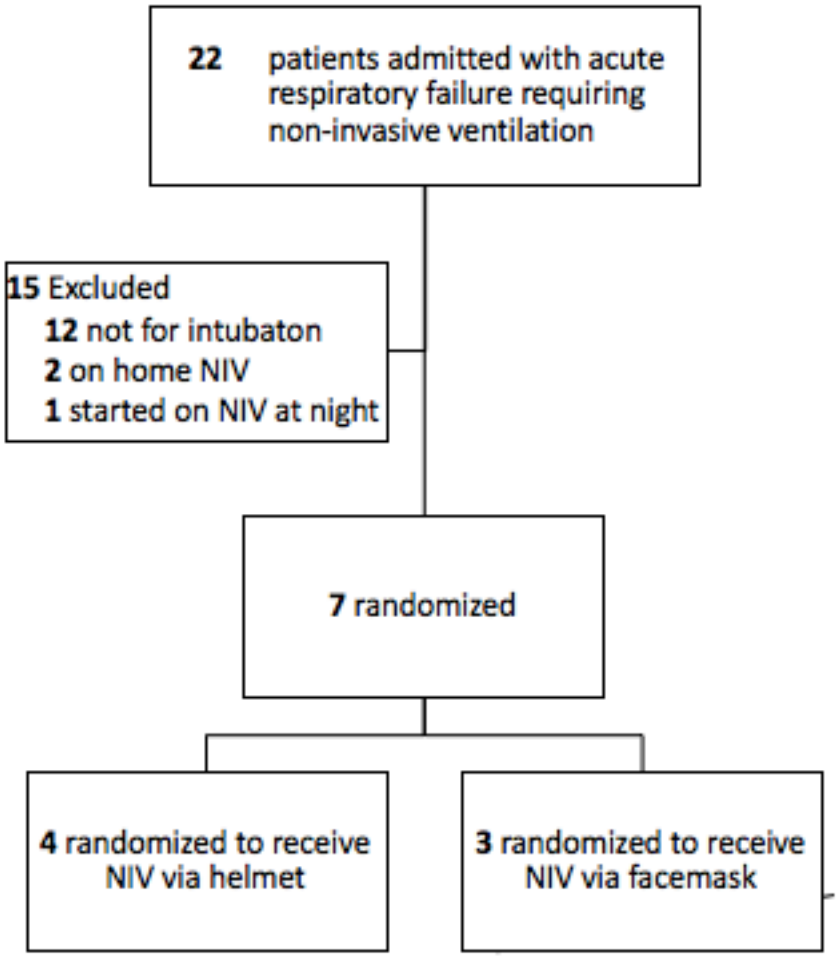
Table 1 – Baseline Characteristics of Patients

	No. (%) of patients receiving NIV	
Characteristic	**Helmet NIV (n = 4)**	**Facemask NIV (n=3)**
Age, median (IQR), y	75 (70.5 – 78)	72.5 (64 – 81)
Women	3 (75)	1 (33)
Black	0 (0)	0 (0)
White	4 (100)	3 (100)
Hispanic	0 (0)	0 (0)
Asian	0 (0)	0 (0)
South Asian	0 (0)	0 (0)
Indigenous	0 (0)	0 (0)
APACHE II[1], median (IQR)	20.5 (15 – 24.5)	12 (10 – 31)
Medical History		
Cirrhosis	0 (0)	0 (0)
Congestive Heart Failure	0 (0)	1 (25)
Coronary artery disease	1 (25)	0 (0)
Asthma	0 (0)	1 (25)
Chronic obstructive pulmonary disease	0 (0)	0 (0)
Diabetes Mellitus	1 (25)	1 (25)
Smoker	0 (0)	0 (0)
Active cancer	2 (50)	2 (67)
Other Immunocompromised state[2]	2 (50)	0 (0)
Reason for Acute respiratory Failure		
Pulmonary edema	1 (25)	0 (0)
Pneumonia	1 (25)	1 (33)
Pulmonary neoplasm	1 (25)	1 (33)
Pleural effusion	0 (0)	1 (33)
Pulmonary embolism	1 (25)	0 (0)
Respiratory and Hemodynamic Parameters, Median (IQR)		
Type of support before NIV		
High flow nasal cannula (HFNC)	1 (25)	1 (33)
Facemask/Venturi mask	3 (75)	1 (33)
None	0 (0)	1 (33)
Respiratory rate, median (IQR)	31 (29.5 – 32.5)	24 (23 – 25)
Heart rate, median (IQR)	124 (95 – 128)	128 (115 – 132)
SpO2, median (IQR)	92 (91.5 – 95.5)	96 (93 – 97)
FiO2, median (IQR)	50 (45 -70)	60 (40 – 75)

Table 2 – Level of physiological support with NIV

	Non-invasive Ventilation (Median (IQR)	
Respiratory support	**Helmet (n = 4)**	**Facemask (n=3)**
PEEP (cm H20)	10 (8 – 10)	9 (8 – 10)
Pressure Support (cm H2O)	14.5 (13 – 15.3)	18 (18 – 18)
FiO2 (%)	50 (36.3 – 67.5)	30 (21 – 30)
SpO2 (%)	96 (93.3 – 97.3)	98 (95 – 99)

Figure 1 – Study Flowchart



METHODOLOGICAL ISSUES AND THESIS CONCLUSIONS

Building a research program based on a new health technology during a pandemic meant facing various methodological challenges and determining how to best tackle them. The following illustrates some key methodological issues encountered in each of the three projects above.

Manuscript # 1

Before embarking on a research program in helmet NIV, it was important to assess what had already been done. In the context of a systematic review and meta-analysis (first manuscript), I sought to summarize all the current randomized and observational study data evaluating helmet NIV use. This systematic review enabled me to define what was known and what was unknown or uncertain regarding helmet NIV application in acutely ill patients with respiratory failure. Upon completion of this review, I was able to further define a subsequent research question and begin to build my research program. Furthermore, I hope that this review will provide clarity for clinicians regarding the indications for helmet NIV use and the state of the current evidence.

The systematic review suggested that helmet NIV may reduce intubation and mortality compared to face mask NIV, although this was based on low certainty evidence. Interestingly, this effect was persistent across patients including both hypoxic and hypercapnic respiratory failure. Previous RCTs had only compared helmet NIV to other oxygen modalities for specific conditions, however, our review suggested that perhaps the two NIV modalities should be compared in all patients respiratory failure, regardless of whether it was primarily hypoxemic or hypercapnic .

I encountered a few methodological challenged in conducting this systematic review. First, given that I included both randomized and observational studies, I needed to determine how to best summarize and present the data. Cuello-Garcia et al. [57] identified two circumstances in which non-randomized data can be used alongside randomized studies in systematic reviews: 1) when RCT evidence is deemed of low or very low certainty assessed using GRADE methodology and non-randomized studies will yield evidence equal to or superior to that of RCT evidence or 2) when RCT evidence is of moderate certainty but non-randomized studies could mitigate concerns regarding indirectness of RCT evidence. In our case, even though the RCT evidence was deemed of low certainty, the non-randomized studies were of even lower certainty and did not provide any additional outcomes that were not available through RCT data. Thus, we chose to primarily focus on evidence from RCTs.

Another methodological challenge that I faced in conducting this review was related to the small sample size of the included studies. This raised concerns related to potential publication bias. To address this concern , I constructed funnel plots to assess for asymmetry. Additionally, when assessing the certainty of evidence using GRADE methodology, I rated the certainty down by 2 points based on imprecision related to the extremely small number of events in our critical outcomes of intubation and mortality.

Manuscript 2

I recognized that introducing a new technology, such as helmet NIV, in the intensive care setting would be associated with several challenges. Consequently, I opted to introduce the helmet into the ICUs of 2 healthcare systems first to build familiarity with the use and operation of the device amongst healthcare professionals including intensivists and respiratory therapists. I described our experience in introducing helmet NIV technology into these 2 acute care settings in a case series of 16 patients.

The second manuscript describes our overall experience. I found that the helmet was generally well tolerated across a broad range of patients with ARF. However, I also noted that a larger than anticipated proportion of acutely ill patients ultimately underwent intubation. Although this study showed that introduction and use of this technology was possible in 2 ICUs in North America during the COVID-19 pandemic, it also highlighted the need for additional larger studies to better characterize helmet tolerance, safety, efficacy, cost-effectiveness and overall healthcare worker and patient experience with this new device.

Given the retrospective nature of the data collection, I proposed use of a waived consent model to conduct this study. The helmet device was used in both centres as a clinical tool for patients with ARF, rather than as an intervention in a clinical study. Thus, the choice to use helmet NIV was made by clinicians in real-time and based on clinical considerations and experience/comfort with the device. As a result of the retrospective nature of the data collection, I considered that patient or surrogate consent was not required and proposed this consent model when I sought ethics approval. As a result of the retrospective design, I was not able to prespecify or standardize the data that was collected and I was limited by the data that were collected in individual patient charts.

The small sample size of this case series also limited its applicability. I believe that the small sample size was a result of three major factors: First, introducing a new technology, particularly one that requires some additional training and human resources is very difficult in a critical care setting. Second, new technology is often accompanied by skepticism, especially when initial application can be challenging and is associated with its own issues. In the case of the helmet NIV, the lack of a reliable indicator of tidal volumes, armpit sores, and oral dryness were new challenges that affected belief in helmet NIV efficacy and limited uptake. Third, the COVID-19 pandemic worsened the aforementioned problems. Healthcare worker stress and burnout increased and so did hesitancy regarding introduction of this technology. With a group of colleagues, I attempted to ameliorate these factors with education sessions illustrating the benefits of the helmet, including its decreased potential to spread infection, along with promoting RT and physician feedback and ways to improve the current delivery of helmet NIV. While this in some ways improved uptake of the device in one centre (Juravinski), the other centre unfortunately, due to skepticism regarding the helmet's benefits, opted to stop using the device altogether.

Manuscript 3

With our work on the systematic review, along with building experience and comfort using helmet NIV at the Juravinski Hospital, I decided to proceed with a pilot feasibility RCT

comparing helmet NIV to face mask NIV for patients with ARF of any cause. Data from our review, although limited by certainty estimates, suggested that the helmet device was superior to the facemask device for both hypoxic and hypercapnic respiratory failure with respect to intubation and mortality. Given that previous RCTs on this topic had only examined specific causes of respiratory failure, along with the small sample size of these RCTs, I decided that there was sufficient prior research and justification to proceed with testing the helmet NIV in a broader patient population. through conduct of a feasibility trial in preparation for conducting a large, multi-centre RCT in the future.

The feasibility trial was funded through Hamilton Health Sciences New Investigator Fund and Gala Foundation. At present, we are implementing this pilot trial and addressing important methodological issues as they arise. I highlight some of the issues encountered thus far in the text below:

1. Protocol adherence – One of our main feasibility outcomes is protocol adherence. In the pilot, we have chosen to define adherence to helmet NIV as helmet NIV use for at least 4 hours in the first 24 hours. We chose this short duration recognizing that a significant proportion of NIV patients fail NIV in the first 4 hours [58] and we did not want to exclude this patient population from the trial. However, if a large proportion of patients were to be included who only use helmet NIV for a short duration, it would reduce intervention fidelity and internal validity of the trial. As recruitment in the trial continues enrollment, I will continue to assess protocol adherence.
2. Multicentre expansion –Enrollment in the pilot trial has been hindered by two main factors: 1) introduction of a new technology in the busy ICU setting and 2) healthcare worker burnout, partially as a result of the COVID-19 pandemic. One potential way to expand enrollment would be to consider expansion to a second site or multiple additional sites. However, introducing a new technology trial at multiple sites is expected to be challenging, related to adoption of a new technology along with healthcare worker burnout as the pandemic wanes. In addition, there is significant lag time between introducing the trial idea to a site and beginning enrollment, related to the need to introduce the helmet device, build comfort and experience with it and elicit feedback. Not to mention the normal procedures that are necessary for site expansion (i.e. general approval processes including local REB approval, engaging local investigators, ensuring research capacity etc.). Finally, addressing questions and troubleshooting problems arising about the interface at a site where the PI does not work is logistically challenging. We hope that by conducting a multicentre pilot feasibility trial first, we are able to smooth out some of these issues before the larger trial.
3. Knowledge translation - I plan to publish the results of both the pilot trial and the larger trial (if conducted) in a scientific journal and presenting it at national and international critical care conferences (SCCM, ESICM). I will report on feasibility metrics in the pilot trial. I plan to update our systematic review with the results of our larger trial. This information can then serve to inform the creation of knowledge tools such as clinical practice guidelines regarding the use of helmet NIV. To implement this knowledge, the important stakeholders must first be identified. In this case, they will primarily be intensivists, other physicians working in the ICU, emergency physicians, RT's in North America and respirologists. Publishing the study and presenting it at conferences will be

the first step to disseminating the results of this study. In addition, the study results will also be disseminated electronically through Twitter, medicine blogs (EMCrit, PulmCrit) and podcasts by the authors of the study.

Conclusions

The overarching goal of this thesis was to examine the efficacy and safety of the helmet NIV in acute respiratory failure in the ICU. I started by a comprehensive systematic review and meta-analysis on the topic, comparing helmet NIV to bilevel NIV and HFNC. The results of the analysis led to a hypothesize that helmet may be superior to facemask for a variety of patients presenting with ARF. To begin to test this hypothesis, I first introduced helmet NIV into 2 ICUs, and launched a feasibility RCT. Demonstration of our ability to achieve feasibility metrics, will determine whether we can proceed to a larger RCT to assess the impact of helmet NIV against bilevel NIV for patients with hypoxemic or hypercapnic ARF.

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