

Non-invasive mechanical ventilation weaning protocols: a systematic review

Protocolos para desmame da ventilação mecânica não invasiva: uma revisão sistemática

Protocolos para el destete de la ventilación mecánica no invasiva: una revisión sistemática

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ABSTRACT | The aim of this study was to perform a systematic review of studies that investigated non-invasive ventilation (NIV) weaning protocols in adult or hospitalized elderly individuals. Through a systematic review based on the Prisma protocol, studies of eight databases published in Portuguese, English or Spanish were considered. The primary outcomes of this review were the success rate of NIV weaning, NIV duration and duration of intensive care unit (ICU) and hospital stay, and secondary endpoint were adverse events associated with protocols for NIV weaning. The methodological quality of clinical trials was assessed using the PEDro scale and for observational studies the Dows and Black scale. Four of the 18,476 initial references met the inclusion criteria and were included in this review. Two of the four articles were randomized clinical trials and two were observational studies. The studies assessed elderly patients with respiratory failure, mainly due to exacerbation of chronic obstructive pulmonary disease (COPD), and acute cardiogenic pulmonary edema. High weaning success rates were observed in three of the four studies, and one study demonstrated the superiority of implementing an immediate protocol for weaning to reduce NIV duration and ICU stay. However, because of the heterogeneity and poor methodological quality of the studies, it is not possible to make recommendations on the implementation of weaning protocols in this population.

Keywords | Non-invasive Ventilation; Positive-Pressure Respiration; Protocols; Weaning; Ventilator Weaning.

RESUMO | O objetivo deste trabalho foi realizar revisão sistemática de estudos que investigaram protocolos de desmame da ventilação não invasiva (VNI) em indivíduos adultos ou idosos hospitalizados. Por meio dessa revisão, baseada no protocolo Prisma, foram selecionados estudos de oito bases de dados publicados em português, inglês ou espanhol. Os desfechos primários desta revisão foram taxa de sucesso de desmame da VNI, duração da VNI e duração da permanência na unidade de terapia intensiva (UTI) e no hospital, e como desfecho secundário foram considerados os efeitos adversos associados aos protocolos de desmame da VNI. A qualidade metodológica dos ensaios clínicos foi avaliada por meio da escala PEDro, e a escala de Downs e Black foi utilizada para a avaliação dos estudos observacionais. Das 18.476 referências iniciais, quatro atenderam aos critérios de inclusão e foram incluídas nesta revisão. Dois dos quatro artigos eram ensaios clínicos randomizados e os outros dois eram estudos observacionais. Os estudos envolveram pacientes idosos com insuficiência respiratória, principalmente por exacerbação da doença pulmonar obstrutiva crônica (DPOC) e edema agudo de pulmão cardiogênico. Foram observadas elevadas taxas de sucesso de desmame em três dos quatro estudos, e um destes demonstrou a superioridade da implementação de um protocolo de desmame imediato na redução da duração da VNI e da permanência na UTI. No entanto, devido à heterogeneidade e à baixa qualidade

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metodológica dos estudos, não foi possível fazer recomendação sobre a implementação dos protocolos de desmame nessa população.

Descritores | Ventilação não Invasiva; Respiração com Pressão Positiva; Protocolos; Desmame; Retirada do Respirador.

RESUMEN | El objetivo de este trabajo ha sido realizar una revisión sistemática de estudios que investigaron protocolos de destete de la ventilación no invasiva (VNI) en individuos adultos o ancianos hospitalizados. A través de esta revisión, basada en el protocolo Prisma, se seleccionaron estudios de ocho bases de datos publicadas en portugués, inglés o español. Los resultados preliminares de esta revisión fueron la tasa de éxito de destete de la VNI, la duración de la VNI y la duración de la estancia en la unidad de cuidados intensivos (UCI) y en el hospital, y como resultado secundario se consideraron los efectos adversos asociados a los protocolos de destete de la VNI. La calidad metodológica de los ensayos clínicos ha sido evaluada a través de la escala PEDro, y la escala de Downs y Black ha sido utilizada

para la evaluación de los estudios observacionales. De las 18.476 referencias iniciales, cuatro cumplieron los criterios de inclusión y se incluyeron en esta revisión. Dos de los cuatro artículos consistían en ensayos clínicos aleatorizados y los otros dos consistían en estudios observacionales. Los estudios incluyeron pacientes ancianos con insuficiencia respiratoria, principalmente por exacerbación de la enfermedad pulmonar obstructiva crónica (EPOC) y edema agudo de pulmón cardiogénico. Se observaron elevadas tasas de éxito de destete en tres de los cuatro estudios, y uno de éstos demostró la superioridad de la implementación de un protocolo de destete inmediato en la reducción de la duración de la VNI y de la permanencia en la UTI. Sin embargo, debido a la heterogeneidad y a la baja calidad metodológica de los estudios, no se pudo hacer recomendación sobre la implementación de los protocolos de destete en esa población.

Palabras clave | Ventilación no Invasiva; Respiración con Presión Positiva; Protocolos; Destete; Retirada del Respirador.

INTRODUCTION

Non-invasive mechanical ventilation (NIV) is considered a therapeutic option for the treatment of numerous clinical conditions, such as acute cardiogenic pulmonary edema (ACPE), exacerbation of chronic obstructive pulmonary disease (COPD), moderate and severe asthmatic attacks, adult respiratory distress syndrome, pneumonia, post-operative and weaning from mechanical ventilation¹⁻⁹. It presents different degrees of recommendation for these conditions and is considered as level of evidence A for the treatment of ACPE and exacerbation of COPD^{10,11}.

Although there are recommendations for the implementation of NIV^{10,11}, there are no guidelines for weaning from this type of ventilation. In 2008, the Royal College of Physicians (RCP) and the British Thoracic Society (BTS)¹² suggested a weaning protocol for NIV. However, this was not adopted as a guideline, in addition to not being followed worldwide. Usually, the weaning process of NIV is performed through the clinical judgment of the team involved and it is based on parameters, such as clinical improvement, heart rate, respiratory rate, level of consciousness and analysis of complementary exams¹³.

One of the reasons for the lack of guidelines for NIV weaning may be that, unlike endotracheal intubation, it is considered easy to withdraw the patient from NIV and return the patient to it several times a day without causing harm. Thus, there is a tendency to prolong the duration of NIV, which can lead to prolonged hospital stay, increased hospital infections and, therefore, increased costs. On the other hand, early NIV weaning may also occur, which may lead to degradation of the patient's clinical status condition and increase the incidence of intubation¹³. For this reason, it is necessary to investigate NIV weaning protocols.

In this context, this article aimed to conduct a systematic review of clinical studies that investigated NIV weaning protocols in adults or hospitalized elderly individuals.

METHODOLOGY

Type of study

This is a systematic review that was performed according to the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)¹⁴.

Eligibility criteria

The following inclusion criteria were considered: (1) participants: hospitalized individuals aged 18 years or older of both sexes; (2) type of intervention: VNI weaning protocol; (3) comparisons: (a) studies describing weaning protocols; (b) studies comparing two or more weaning protocols; (4) study design: (a) randomized controlled trials (RCTs); (b) quasi-experimental studies; (c) observational studies. Articles in Portuguese, English and Spanish languages were considered. Review articles, case studies, monographs, studies published only as annals of scientific events, chapters, guidelines, books and specialists' point of views were excluded.

Primary Outcomes

NIV weaning success rate; NIV duration; duration of ICU and hospital stay.

Secondary outcome

Adverse effects associated with NIV weaning.

Sources of information

The search was performed from October 2015 to December 2015 in eight databases: MEDLINE (via PubMed and via OvidSP), PEDro, LILACS, SciELO, COCHRANE, CINAHL, Web of Science and Scopus retrospectively until their year of creation.

Search strategy

For the article search, the descriptors selected were based on the MeSH or DeCS terms, as well as other descriptors of articles with similar themes. The following search strategy was performed on the MEDLINE database via PubMed: (“Noninvasive Ventilation”[Mesh]) OR (“Positive-Pressure Respiration”[Mesh]) OR (“Continuous Positive Airway Pressure”[Mesh]) OR (“non-invasive ventilation”[tiab] OR “non invasive ventilation”[tiab] OR “NIV”[tiab] OR “non-invasive positive pressure ventilation”[tiab] OR “non invasive positive pressure ventilation”[tiab] OR “noninvasive positive pressure ventilation”[tiab] OR “NIPPV”[tiab] OR “CPAP”[tiab] OR “bi-level positive airway pressure”[tiab] OR “bi level positive airway pressure”[tiab] OR “bilevel

positive airway pressure”[tiab] OR “BIPAP”[tiab] OR “non-invasive ventilatory support”[tiab] OR “non invasive ventilatory support”[tiab] OR “noninvasive ventilatory support”[tiab]) AND (“Weaning”[Mesh]) OR (“Ventilator weaning”[Mesh]) OR (“withdrawal”[tiab]). Journals of the area, theses and dissertations, as well as bibliography of existing revisions on NIV and the studies included in the review were manually searched.

Data selection and extraction processes

Two reviewers independently traced the title and abstract of each study. All potentially relevant articles were retrieved in full text form for evaluation by the two reviewers. In cases of disagreement, a third evaluator also independently participated in the evaluation. Data were extracted independently by two examiners using a standardized extraction form.

Quality assessment

For the clinical trials, the quality assessment was performed using the PEDro scale (www.pedro.org.au) and for the assessment of the observational studies, the Downs and Black¹⁵ scale was used. This scale is composed of 27 items distributed in five subscales that cover reported information; external validity; internal validity (bias and confusion) and power. The maximum score is 31 points. The quality of the studies was evaluated by two independent evaluators and, in case of disagreement, a third evaluator also participated in the process independently.

Synthesis of results

A narrative synthesis of the data was used. The data were tabulated through tables comparing studies for their characteristics, characteristics of the population and the protocols used. A discussion on the impact of the methodological quality of the studies was conducted.

RESULTS

Figure 1 summarizes the identification and selection process that resulted in four studies¹⁶⁻¹⁹ included in the review.

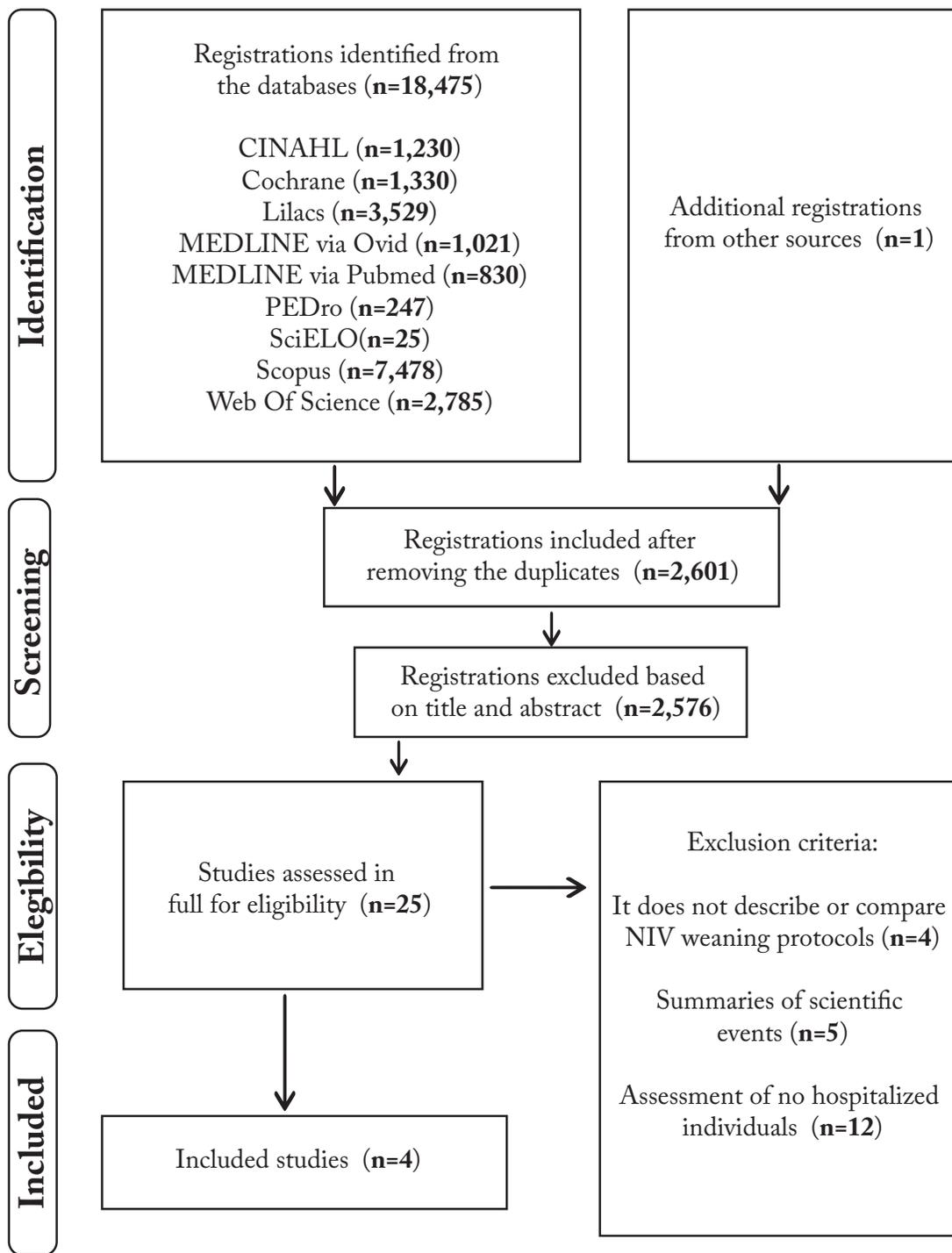


Figure 1. Flowchart of search and selection of studies

Description of studies

The protocols used in the four included studies, as well as the criteria for initiating NIV weaning, are described in Table 1. Lun et al.¹⁶ compared two weaning protocols, a progressive one and an immediate one, and

Duan et al.¹⁷ compared one immediate weaning protocol with the withdrawal of NIV based on the decision of the medical team. On the other hand, in the studies of Damas et al.¹⁸ and Mommi et al.¹⁹, progressive weaning protocols were described. In all studies, NIV was used in bilevel mode.

Table 1. Description of protocols

Authors	Description of protocol	Weaning criteria
Lun et al. ¹⁶	<i>Progressive weaning protocol (G):</i> NIV duration was reduced to 16 hours on day of randomization (day 0) and then reduced to 12, 8 and 0 hour (s) on days 1, 2 and 3, respectively. <i>Immediate weaning protocol (G2):</i> patients were weaned as soon as they were randomized to the group.	pH>7.35 and clinical stability.
Duan et al. ¹⁷	<i>Protocol-based weaning (G1):</i> Respiratory therapists disconnected patients from NIV and offered O ₂ (via NC up to 5L/min), after reaching criteria for weaning. <i>Weaning based on medical team decision (G2):</i> Patients weaned from NIV only after authorization and recommendations from the medical team.	pH≥7.30; FiO ₂ ≤0.5; PaO ₂ >60 mmHg; PaO ₂ /FiO ₂ >150; SaO ₂ ≥92%; RF of 8 irpm at 30 irpm; Systolic blood pressure from 90 mmHg to 180 mmHg without vasopressor; T° from 36°C to 38°C; HR from 50 bpm to 120 bpm; ECG≥13.
Damas et al. ¹⁸	<i>Progressive weaning protocol:</i> Day 1 – During the day: every 3 hours, 1 hour without the use of NIV and 2 hours with it. Night period: NIV continuously. Day 2 – During the day: every 3 hours, 2 hours without NIV and 1 with NIV. Nocturnal period: continuous use of NIV. Day 3 – During the day: without the use of NIV (only with the use of O ₂) and at night they were using NIV. O ₂ administered to achieve SpO ₂ ≥90% (between 6 and 15 L/min).	pH≥7.35 and HR<25 irpm for 24 hours.
Momii et al. ¹⁹	<i>Progressive weaning protocol:</i> Once SpO ₂ remained ≥99% for 30 min, in the first step, FiO ₂ was decreased by 20% every 30 minutes, if SpO ₂ ≥95%, until it reached 40%. If the patient's condition remained stable for 30 minutes, IPAP and EPAP were decreased by 3cm of H ₂ O every 30 minutes while SpO ₂ was maintained above 95%. If SpO ₂ remained above this value for another 30 minutes, the NIV was removed and O ₂ was administered via NC.	SpO ₂ ≥99%, absence of signs of respiratory effort and BP and HR abnormalities for 30 minutes.

NC – nasal cannula; ECG – Glasgow coma scale; EPAP – expiratory positive airway pressure; HR – heart rate; FiO₂ – inspired fraction of oxygen; RF – respiratory frequency; G – group; IPAP – inspiratory positive airway pressure; O₂ – oxygen therapy; BP – blood pressure; PaO₂ – arterial oxygen pressure; SpO₂ – peripheral saturation of hemoglobin in oxygen; T° – body temperature; CV – current volume; VM – volume per minute; NIV – non-invasive ventilation

Table 2. Characteristics of the studies

Authors	N	Diagnosis	Age (YeaRS)	Comparisons	Results
Lun et al. ^{16*}	60 (G1=35; G2=25)	Exacerbation of COPD	G1: 75.3±9.0 G2: 73.9±9.0	Progressive weaning protocol (G1) versus immediate weaning protocol (G2)	There was no statistically significant difference in weaning success rate (G1: 74.3% versus G2: 56%, p=0.139). Significantly lower NIV duration in G2 (median of 0, IQ: 0-3) vs G1 (median of 3, IQ: 3-3) (p<0.001). There was no significant difference between G1 (median of 5, IQ: 5-7) and G2 (median of 5; IQ 3-6.5) for hospital stay (p=0.14).
Duan et al. ^{17*}	73 (G1=37; G2=36)	COPD exacerbation (n=47); Pneumonia (n=18); Asthma (n=5); Others (n=3)	G1: 71.3±12.3 G2: 71.8±13.5	Protocol-based weaning (G1) versus weaning based on the decision of the medical team (G2)	The lowest duration of NIV (2.6±1.5 versus 4.4±2.5, p<0.001) and ICU stay (5.8±2.5 versus 8.1±5.5, p=0.02) for G1.
DAMAS et al. ¹⁸	65	Acute chronic respiratory insufficiency exacerbated mainly by exacerbation of COPD	71.9±10.1	Protocol description	Success rate of 83.7%.
Momii et al. ¹⁹	45	Acute cardiogenic respiratory edema	82.6±10.4	Protocol Description	Mean duration of 19.5±28.

COPD – chronic obstructive pulmonary disease; G – group; IQ – interquartile range; ICU – intensive care unit; NIV – non-invasive ventilation. *Randomized Clinical Trials

The characteristics of the studies are described in Table 2. Two of the four articles were RCTs^{16,17} and two were observational studies^{18,19}. The studies involved elderly patients with acute chronic respiratory insufficiency, mainly due to exacerbation of COPD and ACPE. The sample size ranged from 45 to 73 patients.

Methodological Quality

The study by Lun et al.¹⁶ received a score of 7/10 and the study by Duan et al.¹⁷ of 5/10. Both studies did not present masking of participants, therapists and examiners, and in the study by Duan et al.¹⁷ no blinding was also performed on allocation and intention-to-treat analysis. The scores obtained for the observational studies were 10/31 for the study by Damas et al.¹⁸ and 13/31 for the study by Mommi et al.¹⁹. In these studies, limitations were observed regarding the description of outcomes and study findings; the representativity of the sample investigated; internal validity (absence of blindness of evaluators and subjects, lack of appropriate statistical tests, absence of randomization and adjustment of confounding factors) and power.

Primary Outcomes

Weaning success rate

This outcome was considered primary in the study by Lun et al.¹⁶, who did not find a statistically significant difference between the groups of progressive (74.3%) and immediate (56%) weaning protocols. In the study of Duan et al.¹⁷, in the weaning protocol group, the weaning success rate was 57%, 27%, 13%, 0% and 3% on the 1st, 2nd, 3rd, 4th and 5th days after randomization, respectively. Regarding the observational studies, Damas et al.¹⁸ reported weaning failure in 16.3% of the patients. On the other hand, Mommi et al.¹⁹ did not evaluate this outcome.

NIV duration

This outcome was considered primary in the study by Duan et al.¹⁷, who compared protocol-based weaning to weaning guided by the medical team. The study demonstrated that the group weaned from NIV via a protocol had a statistically significant reduction in NIV duration. In the study by Lun et al.¹⁶, NIV mean duration after randomization was significantly

lower in the group submitted to the weaning protocol, as expected. In the study by Mommi et al.¹⁹, NIV mean duration was 19.5±28 hours. Damas et al.¹⁸ did not report results for this outcome.

Duration of ICU and hospital stay

These outcomes were considered secondary in both RCTs. In the study by Duan et al.¹⁷, the weaning protocol group presented a significant reduction in the duration of ICU stay compared to the group whose weaning was performed by the medical team. On the other hand, Lun et al.¹⁶ did not find a statistically significant difference for the duration of hospital stay between the groups submitted to the progressive versus immediate weaning protocol. The observational studies did not report these outcomes.

Secondary outcome

Adverse effects

In none of the studies included in the review, a specific adverse effects analysis was performed.

DISCUSSION

This systematic review found only four studies investigating the use of NIV weaning protocols in hospitalized patients¹⁶⁻¹⁹ and only two of them were RCTs^{16,17}. All studies evaluated adult or elderly individuals, three of which included patients with COPD exacerbation and one evaluated subjects with cardiogenic ACPE. There was no consent in the studies concerning the outcomes evaluated and the protocols investigated.

One of the RCTs included in this review demonstrated the superiority of protocol-based weaning performance with regard to NIV duration as well as ICU stay¹⁷. Protocol-based NIV weaning significantly reduced these outcomes when compared to weaning guided by medical team. These results reinforce that the absence of weaning protocols can prolong the duration of hospitalization, with consequent increase in the risk of infections as well as associated costs¹³.

Regarding the weaning success rate, studies by Duan et al.¹⁷ and Damas et al.¹⁸ demonstrated high weaning success rates independently of the used protocol, which was immediate in the case of the study by Duan et al.¹⁷ and progressive in the study by Damas et al.¹⁸. In

this perspective, Lun et al.¹⁶ did not find a statistically significant difference for the weaning success rate between the group submitted to the progressive weaning protocol and the group submitted to immediate weaning. One of the reasons for this finding may have been the sample size of this study, considering that the statistical power for this outcome was only 43.6%.

Regarding the weaning protocols presented, three^{16,18,19} of the four included studies adopted progressive weaning protocols, similarly to that proposed by RCP/BTS¹² and two investigated protocols for immediate weaning^{16,17}. However, there is great variation in the weaning progression. In the study by Duan et al.¹⁷, patients were submitted to immediate weaning from NIV as soon as they met the weaning criteria and were placed in oxygen therapy. Patients in the study by Lun et al.¹⁶ who underwent immediate weaning protocol were immediately withdrawn from NIV after randomization in the group and the authors did not mention supplemental O₂ supply. On the other hand, the group in the study of Lun et al.¹⁶ who underwent progressive protocol, the reduction of NIV supply occurred over three days with a gradual reduction in NIV supply time on each day. However, the authors did not mention the progression of pressure parameters and the control of peripheral saturation of hemoglobin in oxygen (SpO₂) during the process. In the study by Damas et al.¹⁸, the weaning progression was also performed over three days, and the reduction of NIV occurred gradually during the day and patients were remained in NIV overnight. And at the time of day without NIV, oxygen therapy was offered to maintain SpO₂ ≥90%. On the other hand, in the study by Momii et al.¹⁹ the SpO₂ values served as the initial basis for the reduction of the inspired fraction of oxygen (FiO₂) and as soon as the patients maintained SpO₂ ≥95% with FiO₂ of 40%, the authors progressively reduced the NIV pressure values until its withdrawal. As in the study by Damas et al.¹⁸, patients received supplemental O₂ when out of NIV. In addition, as demonstrated in the protocol description table, there was variation regarding the criteria used by the authors to initiate weaning from NIV.

In addition to the heterogeneity regarding the investigated protocols and the design of the studies, an important finding of this review concerns the methodological quality. Some weaknesses have been observed, which may compromise the internal validity of the studies. Both included RCTs^{16,17} did not have masked subjects and evaluators. In addition, in the study by Duan et al.¹⁷, no “intention-to-treat” analysis was performed and

the subjects’ distribution in the groups was not blinded. Potentially, if the distribution is not blind, the decision whether to include the subject in the study or not can be influenced by prior knowledge of the group to which the subject will be allocated. This can produce systematic deviations in the random distribution. Additionally, the observational studies presented low scores on the methodological scale of Downs and Black¹⁵, with limitations both in respect to internal validity and external validity.

This review has some limitations. One of them is scarcity of adequate methodological quality RCTs that investigated the efficacy of the use of NIV weaning protocols in hospitalized individuals. There was a fragility in the internal validity of the studies, since important strategies to minimize bias risks were not employed. In addition, a recent RCT published in abstract²⁰ form could not be included in the review. The authors of the study were contacted, and they reported that the work had not been fully published so far. From the analysis of the abstract, we found that the authors did not find statistically significant differences between the NIV immediate weaning and a protocol of three additional nights of NIV for weaning success outcomes, hospital stay duration and mortality in COPD patients after an episode of acute respiratory failure. However, it was not possible to access the detailed study information.

CONCLUSION

This systematic review demonstrates the paucity of available evidence on NIV weaning protocols in hospitalized adult or elderly individuals. High success rates of weaning protocols were observed and only one study demonstrated the superiority of implementing an immediate weaning protocol in reducing NIV duration and ICU stay. However, due to the heterogeneity of the protocols and the fragility of most of the studies, it is not possible to make recommendations on the implementation of weaning protocols in this population.

Thus, randomized controlled trials with more methodological rigor need to be performed. Further research on the impact of these protocols on clinical practice is necessary to avoid possible risks due to their inadequate application, prolonged use of technique and/or weaning, increased length of hospital stay, increased occurrence of hospital infections and increased hospital costs.

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