EFFECTIVENESS OF COUGH ASSIST IN THE EXTUBATION OF ADULT PATIENTS: SYSTEMATIC REVIEW AND META-ANALYSIS

Giulia Montigiani 1; Davide Papi1; Lorenzo Proietti1; Beatrice Meucci 2; Mara Taddei1; Luca Bucciardini1; Mauro Di Bari4.

1PT - Rehabilitation Service, Department of Healthcare Professionals, Azienda Ospedaliero-Universitaria Careggi, Florence – Italy
2RN - Neuro Intensive Care Unit, department of Anesthesia and Intensive Care, Azienda Ospedaliero-Universitaria Careggi, Florence – Italy
3MD - Neuro Intensive Care Unit, department of Anesthesia and Intensive Care, Azienda Ospedaliero-Universitaria Careggi, Florence – Italy
4MD, PhD, - Geriatric Intensive Care Unit, Department of Medicine and Geriatrics, Azienda Ospedaliero-Universitaria Careggi, Florence – Italy

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INTRODUCTION

Removal of an endotracheal tube, even if conducted with standard techniques, may present significant complications, at the time of the procedure as well as subsequently. Extubation failure, resulting in the need for reintubation, may occur in 2-25% of patients undergoing extubation [1]. It has been shown that ineffective cough and abundance of secretions are frequent causes of extubation failure, which may occur in spite of a successful outcome of the spontaneous breath test [2]. Prolonged bed rest, administration of sedatives, and persistence of airway inflammation may concour to bronchial encumbrance, thus reducing the chances of successful extubation [3].

Cough assist is an airway clearance device that, thanks to the inspiratory and expiratory flow, may represent a valuable aid to help patients with ineffective cough eliminate secretions and facilitate bronchial clearance, replacing physiological cough. Although this technology has been introduced in the routine management of many chronic respiratory diseases, its use in the acute setting, and specifically in critical area to ease extubation, has been poorly explored. A few studies examining this topic were limited by the small sample size; therefore, this technique has not been established in current guidelines of extubation.

The purpose of this review and meta-analysis was to determine the effectiveness of cough assist in improving success rates of extubation compared with standard treatment. The inclusion criteria were: Randomized Control Trials, which compared cough assist and conventional therapy in adult population in intensive care unit with conventional therapy only. Outcomes representing the efficacy of the cough assist were: quantity and quality of secretions (weight, volume, and density), number of reintubation, indices of thoraco-pulmonary function.

METHODS

Data sources and search strategy

The study followed the PRISMA checklist. The quality of the included studies was assessed with the Cochrane risk of bias (ROB2) tool for randomized trials.

A systematic literature search of medical literature was undertaken, consulting the PubMed (MEDLINE), EMBASE, Cochrane database of systematic reviews, CINAHL, and PROSPERO databases for studies published until 31 July 2021.
The research string included a combination of the following keywords and connectors: ("Cough * assist "* OR "cough * augment "* OR "in-exsufflat "* OR "insufflat * exsufflat "* OR "MI-E" OR "mechanic * insufflat * exsufflat "* OR "airway clearance device" OR "mechanic * insufflat "* OR "mechanic * exsufflat "* OR "mechanic * cough" OR "cough * aid "* ) AND (extubat "* OR "intensive care unit" OR "artificial air way" OR "ventilat * weaning" OR "impaired air way clearance " OR "endotracheal tube" OR "intubat "*) NOT pediatr "* NOT child "*

Study selection
Two authors (LP and GM) examined independently the studies for eligibility, according to the following criteria:

- Randomized Clinical Trial (RCT) design, with either parallel arms or crossover.
- Participants aged ≥18 years.
- Admission to an Intensive Care Setting.
- Presence of orotracheal tube.
- Mechanical ventilation for at least > 24 h.
- Experimental intervention represented by cough assist, alone or in addition to conventional therapy.
- Control treatment represented by chest physical therapy and/or endotracheal suctioning and/or NIV.

Except for COVID-19, which was considered as an exclusion criterion, all diagnoses were accepted.

Outcomes
Outcomes representing the efficacy of the cough assist were selected: quantity and quality of secretions (weight, volume, and density), reintubation, and indices of thoraco-pulmonary function, such as airway resistance and static compliance.

Statistical analysis
Crossover studies were analyzed as parallel arms RCT. Outcome measures represented by continuous variables, collected at the end of the intervention, were extracted as mean±SD, separately for the experimental and the control groups, and reported on an electronic form. Where measures were reported as median and interquartile range, mean and standard deviation were calculated as \((q1+ \text{median}+q3)/3\) and \((q3-q1)/1.35\), respectively. Cohen’s d estimator, representing the effect size (ES) of the intervention as the difference in the final values in each study group divided by their pooled SD, was calculated, together with its 95% confidence interval (CI). For the dichotomous outcome “reintubation”, the relative risk (RR) was calculated, with corresponding 95% CI.

The results of the different studies were combined according to the Der Simonian-Laird random effects model. Non-cumulability (heterogeneity) of results between different studies was assessed using the Cochrane Q test.

Data analysis was conducted with the Stats direct software. Protection against type I error was set at \(\alpha = 0.05\).

RESULTS
The search string produced 764 studies, of which 737 were excluded after reading title and abstract, with full agreement between the two independent researchers. Out of the 27 studies examined in full-text, the same researchers fully agreed on exclusion of 22 articles, because they did not fulfill the selection criteria: thus, 5 studies were eventually considered eligible for the review (Figure 1).

The 5 studies selected for the meta-analysis were published between 2016 and 2018 and included 3 parallel arms RCTs [4, 5, 6] and 2 crossover studies [7, 8]. Overall, they enrolled a total of 331 participants (Table 1), with sample sizes ranging from 10 and 180 individuals in the individual studies. All patients were aspirated as needed and after cough assistant treatment. Participants in the control group received respiratory physiotherapy and manual cough assistance in all studies but one [8], in which only bronchial aspiration was performed. Moreover, Goncalves performed non-invasive ventilation as needed in both groups (Table 1).

Of the different outcomes considered the five included studies, secretion weight or volume, reintubation, airway resistance, and static compliance were evaluated in this review (Table 1).
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The methodological quality of the studies (Figure 2) was assessed with the Cochrane risk of bias tool for RCTs. No study clearly specified blinding of the investigator. Four studies [4, 5, 7, 8] were free of attrition bias, whereas again four [4, 5, 6, 8] were found to be at low risk of reporting bias. In one study [8] results on dynamic lung compliance outcomes and pulmonary resistance were not described completely. No study provided information to evaluate other types of bias, so that the evaluation in this case was “unclear”.

Table 1: Summary table of the characteristics of the included studies with: population, intervention, control, outcome.

Meta-analysis
Assignment to treatment with cough assist, evaluated in 3 studies, increased significantly secretion weight, as indicated by an ES (95% CI) of 0.49 (0.25, 0.72), which was associated with a p value <0.001 and low heterogeneity (Q = 0.99, p = 0.600) (Figure 3). On the contrary, cough assist did not reduce the risk of reintubation, considered in 2 studies, as assessed from a pooled relative risk of 0.73 (0.14, 3.89), with p = 0.71 and some heterogeneity (Q = 3.41, p = 0.06) (Figure 4). Also the results on airway resistance and compliance, both considered in 2 studies, were non-significant, as indicated by ESSs of -0.25 (-0.53, 0.02) with p = 0.07 and no heterogeneity (Q = 0.04, p = 0.83) and of 0.05 (-0.22, 0.33) with p = 0.71 and no heterogeneity (Q = 0.18, p = 0.67), respectively.
This meta-analysis of 5 RCTs shows that the cough assist device is effective in increasing the amount of secretions removed from the bronchial tree in adult patients with prolonged intubation and mechanical ventilation. Decrease in airway resistance was close to statistical significance, whereas no significant difference was observed in change in compliance and in risk of reintubation. The search for predictors of extubation failure is a major topic in ICU research. It is estimated that, among patients with prolonged ICU stay, about 85% have failed extubation, with a consequent increase in comorbidity and costs [9]. Excess secretions have been lengthy recognized as an important factor in the outcome of extubation [10, 11]. Mokhlesi et al. [12] wrote that the evaluation of endotracheal secretions, patient’s mental state and pre-extubation PaCO2 could be used to predict extubation failure even in patients who had successfully passed a spontaneous breathing trial. In substantial agreement, Kulkarni et al. [13] stated that the efficacy of coughing, the reduced amount of secretions and an adequate state of vigilance are necessary prerequisites for successful extubation, and Smina et al. [14] reported that cough capacity, measured objectively, is a major predictor of extubation failure. Other studies underlined that extubation failure is often mediated by an ICU-associated "acquired weakness", which is frequently observed in individuals undergoing prolonged mechanical ventilation and limits at the same time the ability to mobilize adequate air volumes through the lungs and to clear the airways through effective coughing [15].

To overcome the problems associated with poor airways clearance, mechanical cough assist devices have been introduced, with time adapting to a growing range of applications in different rehabilitation areas [16, 17]. In a recent review [9], the utility of cough stimulator tools has been emphasized, to either prevent orotracheal intubation or avoid intubation. On the other hand, evidence is more limited on the use of the cough assist in mechanically ventilated patients. Yet, this issue is increasingly debated, also because of the variety of techniques and applications that have been developed. The device was initially used only in patients unable to produce effective cough because of neuromuscular disorders [18], in whom it represented a real prosthesis, as it completely replaced an absent function. Nowadays, a new and broader vision of cough assist stems from its use in the ICU area, where its task has become supporting a deficient function. Therefore, the time has come to understand if cough assist can be really useful in improving patient’s clinical status and reducing the risk of reintubation [17, 19, 20]. This work was done with this goal in mind. Only five articles, all published between 2012 and 2018, fulfilled our selective search string with no time limit, confirming that the topic has gained relevance only in recent years. The selected articles shared a limited number of outcomes, of which only the amount of secretions gave fully satisfactory results, showing that cough assists effectively improves airways clearance. Airways resistance, which is somehow associated with bronchial secretions, had a positive trend, whereas compliance and reintubation were far from statistical significance. Since reintubation is a major clinical event that must be prevented, it is highly recommended that it be included as an outcome measure in future studies.

It should be noted that insufflation and exsufflation pressures were set in a very wide range, between +40 and -40 cmH2O. This variability might have contributed to the heterogeneity of the findings across the study selected. None of the studies included in the meta-analysis reported adverse effects from the use of the cough assist. Limitations of this study mostly stem from those of the available literature, such as the small number of studies on the topic, the different outcomes across the studies, and the unclear protocol for cough assist application in some studies. Yet, our study represents a first step towards rigorous evaluation on cough assist devices, applied to promote successful extubation in ICU patients: as such, our work draws the current state of the art and suggests the need for future, high quality studies.

**CONCLUSIONS**

New methods and techniques are nowadays actively searched in many centers around the world to improve the outcome of extubation and avoid reintubation. The available literature, systematically reviewed and meta-analyzed in this study, suggests that cough assistant might contribute to successful extubation in ICU patients, by improving airway clearance. Studies with larger sample sizes, clearly defined protocols and outcomes are required to obtain conclusive evidence. We hope that this meta-analysis will stimulate research on this field.
REFERENCES