Evaluating Viola Odorata for Prevention of Mechanical Ventilation-Related Complications: The First Double Blind Randomized Clinical Trial

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Abstract- Endotracheal intubation is a life-saving procedure performed to protect the airway. However, it may lead to significant complications such as edema, granuloma, and strictures. A unified approach for preventing these complications remains elusive. This study aims to compare the efficacy of Pulmicort plus salbutamol (S-P) versus Viola Odorata extract combined with salbutamol (S-V) in preventing intubation-related complications. This study aims to assess the use of Pulmicort combined with salbutamol versus Viola Odorata extract combined with salbutamol for the prevention of intubation-related complications. This randomized clinical trial was conducted on 63 patients under mechanical ventilation due to trauma from 2018 to 2020. Patients were randomly assigned to receive either 2.5 mg of salbutamol via nebulizer every six hours, plus two puffs of 0.5 mg Pulmicort spray, or 10 cc of Viola Odorata syrup twice daily. Ultrasonographic assessments of air leak, tracheal air column diameter, and tracheal wall thickness were performed at baseline and at the time of weaning. The two groups were similar in terms of age and gender distribution (P>0.05). Comparison of baseline and final measurements of tracheal air column diameter, tracheal wall thickness, and air leak revealed a significant increase in both groups (P<0.001). Post-weaning assessments revealed no significant differences between the S-P and S-V groups in any parameters (P>0.05), except for a higher tracheal air diameter in the S-P group (P=0.004). This study found that Viola Odorata extract led to promising outcomes in preventing mechanical ventilation-related complications. Comparisons with Pulmicort revealed no significant differences. These findings, achieved through ultrasonographic evaluations, suggest that Viola Odorata may be a viable alternative for preventing intubation-related complications.

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Introduction

Endotracheal intubation is a life-saving procedure performed under various life-threatening conditions to secure the airway (1). This procedure helps anesthetized or mechanically ventilated patients maintain proper ventilation (2). Despite its crucial benefits, this procedure can lead to significant complications in up to 18% of patients. Acute complications include injury to surrounding tissues and bronchospasm, while delayed complications encompass mucosal injury, edema, granuloma, and tracheal stenosis. Although typically treatable, prolonged endotracheal intubation may cause irreversible sequelae (3,4). Inflammation at the site of

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the endotracheal tube leads to the development of edema and stricture in the surrounding tissues (5,6). Inflammation is a key pathophysiological mechanism in various lung diseases, including asthma, chronic obstructive pulmonary disease (COPD), and bronchitis (7,8).

Short-acting beta-agonist bronchodilators are commonly used to improve respiratory conditions; however, their short half-life, tachyphylaxis, tremors, and tachycardia necessitate alternative treatments (9). Oral corticosteroids (OCS) effectively suppress inflammation; however, their significant adverse effects, including hyperglycemia, hypertension, osteoporosis, and vertebral compression fractures, limit their use (10). Consequently, researchers are exploring alternative treatments, among which inhaled corticosteroids (ICS) have shown promising results. Budesonide nebulizer (Pulmicort) is a potent corticosteroid successfully used to manage asthma, COPD, and bronchitis (9). Although evidence regarding the use of ICS in reducing endotracheal intubation-related complications is limited, most studies support this approach (11).

Viola Odorata has been used as an herbal remedy for various medical conditions, including fever, musculoskeletal pain, cough, eczema, sore throat, asthma, and bronchitis, for a long time (12-14). Its anti-inflammatory, antioxidant, and antibacterial properties make it a suitable candidate for managing various medical conditions, including respiratory-related diseases (15). To the best of our knowledge, no study has evaluated the use of Viola Odorata for preventing complications related to endotracheal intubation.

This study aims to compare the efficacy of Pulmicort combined with salbutamol versus Viola Odorata extract combined with salbutamol in preventing intubation-related complications. This work is reported in accordance with the SCARE criteria (16).

Materials and Methods

Study population

This randomized clinical trial (RCT) involved 63 trauma patients requiring mechanical ventilation, who were admitted to the Intensive Care Unit (ICU) at Alzahra Hospital, affiliated with Isfahan University of Medical Sciences. The ethics committee of Isfahan University of Medical Sciences approved the study (IR.MUI.MED.REC.1398.363), and it was registered in the Iranian Registry of Clinical Trials (IRCT20210516051314N1). The study protocol was explained to surrogate decision-makers, confidentiality was assured, and written consent was obtained. Patients aged 18 to 65 who had been intubated for at least 24 hours were included in the study. Exclusion criteria were failure to complete the therapeutic approach, medication intolerance, previous intubation history, tracheomalacia, airway anomaly, obesity hypoventilation syndrome, recent use of corticosteroids, need for systemic corticosteroids, hemodynamic instability, and smoking. Participants were selected through convenience sampling. Patients were randomized to receive either the combination of salbutamol nebulizer plus Pulmicort nebulizer (S-P) or the combination of salbutamol nebulizer plus Viola Odorata syrup (S-V) using Random Allocation software, matched by APACHE II score. This double-blinded study ensured that neither surrogate decision-makers nor sonologists knew the treatment allocations.

Interventions

The first group received a combination of 2.5 mg/cc salbutamol nebulizer (Ventolin, GSK/UK) every six hours plus 0.5 mg/cc Pulmicort nebulizer (Cobel Darou, Iran) (group S-P). The second group received a similar salbutamol nebulizer treatment and 10 cc of Viola Odorata syrup (Barij Company, Kashan, Iran) twice daily (group S-V). Interventions continued until extubation.

Primary outcomes

Patients' demographic information, including age and gender, was recorded. Air leak was measured weekly using the cuff-leak test. Ultrasonographic studies with a high-frequency linear probe (13-6 MHz) measured air column diameter and tracheal wall thickness. The probe was placed above the suprasternal notch. Normal tracheal wall thickness values are 1.5±0.2 mm for males and 1.2±0.2 mm for females (17). Ultrasonography was performed at baseline and on a weekly basis until extubation.

Statistical analysis

Data were analyzed using SPSS version 28. Descriptive data were represented as mean, standard deviation, absolute numbers, and percentages. Paired t-tests, independent t-tests, and covariance analysis were used for analytical data. A P of less than 0.05 was considered significant.

Results

Data from 68 intubated traumatic patients were

initially assessed, with 66 meeting the inclusion criteria and being randomly assigned to either the S-P group (n=33) or the S-V group (n=33). In the S-P group, 32 patients completed the study, with one excluded due to early weaning. In the S-V group, 30 patients completed the study, with two withdrawn due to hemodynamic instability and one death. The population included 23 females (37.1%) and 39 males (62.9%), with a mean age of 66.19±12.94 years. The S-V group had a mean age of 46.57±14.22 years, with a predominantly male composition (63.3%), while the S-P group had a mean age of 45.84±11.85 years, with a male prevalence of 62.5%. Age (P=0.82) and gender distribution (P=0.94) were statistically similar between groups. Air leakage was significantly greater in the S-P group at baseline (P=0.006). Covariance analysis revealed higher air leakage in the S-P group by the study's end, with significant changes in air leakage observed in both groups (P<0.001). Post-treatment tracheal air column diameter was 8.64 mm in the S-P group and 8.28 mm in the S-V group. Tracheal wall thickness did not differ significantly between groups at baseline (P=0.26) or post-intervention (P=0.33), although both interventions increased tracheal wall thickness (P<0.001). The final air leakage assessment showed a significant baseline difference (P=0.002) but no post-intervention difference (P=0.37). Post-treatment air leakage was 225.10 ml for the S-V group and 241.16 ml for the S-P group, with both interventions resulting in significantly increased air leakage (P<0.001). Detailed information is provided in Table 1.

Table 1. Detailed results. * Paired-T-test ** Independent T-test # COVARIANCE analysis

	At baseline	After the intervention	Differences	*P**
Tracheal air column diameter (mm), mean±standard deviation				
Viola Odorata plus salbutamol	8.17±0.25	8.28±0.24	0.11±0.07	<0.001
Pulmicort plus salbutamol	8.47±0.53	8.64±0.52	0.16±0.07	<0.001
P	0.006**	0.001#	0.012**	
Trachea wall thickness (mm), mean±standard deviation				
Viola Odorata plus salbutamol	2±0.15	2.53±0.17	0.05±0.06	<0.001
Pulmicort plus salbutamol	2.56±0.22	2.10±0.22	0.04±0.06	<0.001
P	0.26	0.33	0.69	
Air leakage (ml), mean±standard deviation				
Viola Odorata plus salbutamol	214.63±11.35	225.10±9.99	10.46±7.57	<0.001
Pulmicort plus salbutamol	228.34±20.80	241.16±24.7	12.81±8.45	<0.001
P	0.002**	0.37#	0.25**	

Discussion

To the best of our knowledge, this study is the first to evaluate the use of the herbal agent Viola Odorata for preventing endotracheal intubation-related complications. We designed a randomized clinical trial (RCT) to compare the commonly used medical regimen of salbutamol plus Pulmicort with a novel approach of salbutamol plus Viola Odorata extract syrup. Our results demonstrate the therapeutic potential of the S-V for preventing intubation-related complications, as it improved air leak and tracheal air column measurements, though it did result in increased tracheal wall thickness. However, the comparison between S-V and S-P regimens showed no significant difference.

A literature review indicates that local inflammatory responses, such as mucosal inflammation, ulceration, and edema, are responsible for most complications of endotracheal intubation (11). Various medications have been investigated to mitigate intubation-related complications like stridor, stricture, and edema. Inhaled corticosteroids (ICS) are the first-line treatment for patients at high risk of adverse effects from endotracheal intubation due to their anti-inflammatory properties, inhibition of leukocyte migration, maintenance of cell membrane integrity, attenuation of lysosome release,

and reduction of fibroblast proliferation and tissue swelling (18-20). Moreover, ICS can be delivered directly to the site without systemic exposure (21).

Abbasi *et al*., assessed the outcomes of nebulized budesonide in critically ill patients on mechanical ventilation, finding promising results in terms of distress, reintubation rates, and desaturation among extubated patients (11). Sun *et al*. conducted a study on COPD patients, evaluating the effects of nebulized Pulmicort on inflammatory markers and arterial gas pressures, with significant reductions in inflammatory markers and an increase in arterial oxygen pressure (8). Another study by Abbasi *et al*., compared air leak volume and mean tidal volume among intubated patients treated with nebulized Pulmicort versus intravenous dexamethasone or placebo, demonstrating superior outcomes for ICS with fewer adverse effects compared to OCS. However, neither corticosteroid impacted hemodynamic status (22).

In this study, we assessed the use of Viola Odorata for the first time in intubated patients, observing promising outcomes in air leak volume, tracheal wall thickness, and tracheal air column measurements post-intervention. Comparison with nebulized Pulmicort showed comparable outcomes. Mulla *et al.,* reported significant clinical improvements in patients with chronic rhinosinusitis treated with Viola Odorata extract (23). Qasemzadeh *et al*., found a significant reduction in coughing in asthmatic patients treated with Viola Odorata plus beta-2-agonist compared to salbutamol alone (14). Koochek *et al*., demonstrated the moderate efficacy of Viola Odorata extract compared to hydrocortisone in preventing formalin-induced lung injury in rats (24). Other studies have shown encouraging results in treating respiratory disorders, such as chronic cough, dyspnea, and pneumonia (25,26).

Lee *et al*., found a significant reduction in hypersensitivity-related markers in allergic mice treated with Viola Odorata (14). Additionally, the methanol extract of Viola Odorata exhibited potent antibacterial activity against respiratory pathogens (27). The anti-inflammatory effect of Viola Odorata plays a crucial role in preventing intubation complications, such as stridor, stricture, and edema, as demonstrated by the anti-inflammatory activity of water-soluble polysaccharides extracted from Viola Odorata (28). The other active ingredients, including essential oils, salicylic acid, flavonoids, and cyclotides, contribute to its anti-inflammatory and antibacterial properties (14,29).

The main limitation of this study was the failure to assess hemodynamic parameters and potential missing confounding variables. Further evaluations are strongly recommended.

This study is the first to assess the use of Viola Odorata compared to nebulized Pulmicort for the prevention of intubation-related complications through the evaluation of airway-related factors, including air leak volume, tracheal air column diameter, and wall thickness. Viola Odorata showed promising outcomes, with no significant differences compared to Pulmicort. These findings were achieved through ultrasonographic evaluations for the first time.

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