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ORIGINAL RESEARCH AIRWAY MANAGEMENT

Efficacy of nebulized lidocaine, salbutamol, and beclomethasone plus salbutamol in post-COVID ARDS patients on non-invasive ventilation; a randomized controlled trial

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ABSTRACT

Objective: To compare the efficacy of nebulized lidocaine, salbutamol, and a combination of beclomethasone plus salbutamol in post-COVID ARDS patients, on non-invasive ventilation.

Methods: This randomized controlled trial was conducted on 81 post-COVID patients receiving non-invasive ventilation diagnosed with mild to moderate ARDS. Recruited patients had complaints of cough, hypoxia, and respiratory distress. Patients were allocated into three groups by lottery method as per treatment: 'Lidocaine group', 'Salbutamol group', and 'beclomethasone + salbutamol group'. They received nebulization four times/day. Improvement in hypoxia was assessed by a rise in PaO_2 from baseline, improvement in respiratory distress was noted by > 10% amelioration in respiratory rate, and cough suppression was assessed on the 'cough severity scale'.

Results: Improvement in hypoxia was 28.6% vs. 13.3% vs. 15% between Group-L vs. Group-S vs. Group-BS, respectively, with P = 0.001. Improvement in respiratory distress was 89% vs. 59% vs. 55%, and cough suppression was 85% vs. 30% vs. 44% between Group-L vs. Group-S vs. Group-BS, respectively, with a significant P-value. Complications were minimal; 7% in Group-L as compared to Group-S (55%) and Group-BS (48%), with a significant P = 0.001.

Conclusion: Lidocaine is found to be more effective than salbutamol and the combination of beclomethasone ± salbutamol in improvement of hypoxia, respiratory distress, and cough suppression with minimal hazardous effects, in post-COVID ARDS patients receiving non-invasive ventilation.

Clinical Trial Number: NCT04979923

Abbreviations: ARDS: adult respiratory distress syndrome, COVID-19: coronavirus 2019 disease, CSI: cough severity scale, IL-1: interleukin-1, HFO: high flow oxygen

Keywords: Lidocaine, Nebulization, Salbutamol, Beclomethasone, Cough, Hypoxia, Respiratory distress, ARDS

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1. INTRODUCTION

In defiance of extensive preventive measures and vaccination,[1] the healthcare system is still burdened with post-COVID multisystem manifestations.[2,3] Approximately 33% of individuals who have recovered from post-COVID ARDS, experiencing damage to the alveoli, endothelial tissues, and lung parenchyma, accounting for 16% of intensive care admissions recently.[8] There are persistent respiratory manifestations in the patients even after recovery from COVID, leading to reduced functional capacity,[4] and from mild cough (56%-77%),[5,6] to severe hypoxic respiratory failure,[7] contributing to a considerably higher mortality rate (66.7%).[8-10] A cough, apparently a trivial symptom, can cause substantial damage with far-reaching consequences.[11] Therefore, by effectively reducing the detrimental effects of ARDS, including cough, respiratory inflammation, and hypoxia, we can substantially alleviate the burden on the healthcare system.

Despite the vigorous research, there is no patent treatment available for COVID and post-COVID manifestations so far[12], and clinicians worldwide are trying to repurpose various existing drugs for its symptomatic treatment and complications.[13,14] Conventional drugs, like nebulized salbutamol and beclomethasone, and/or intravenous steroids used to relieve the respiratory symptoms, but their safety profile is of concern as they have some disadvantages of their own.[15,16] Recently, Malik et al (2020) have hypothesized on some previously available studies, illustrating the remarkable anti-inflammatory properties of local anesthetics like lidocaine.[18-21]

To date, there are no clinical trials available to authenticate the efficacy of nebulized lidocaine in relieving the respiratory symptoms of post-COVID ARDS, like hypoxia, inflammation of the respiratory tract, and cough. Hence, this study aims to compare the efficacy of nebulized lidocaine with conventional drugs like nebulized salbutamol, and a combination of beclomethasone plus salbutamol (Clenil Compositum) in patients with post-COVID ARDS admitted to the ICU.

2. METHODOLOGY

After Ethical approval (227/IRB/SZMC/SZH) from the institutional review board, this double-blinded randomized control trial (NCT04979923) was conducted in the ICU at Sheikh Zayed Hospital Rahim Yar Khan, Pakistan, from August 2021 to December 2023. A sample size of 77 patients was calculated by running a pilot study initially on twenty patients, keeping the power of the study at 80, the confidence level at 95, percentage of cough suppression among the two groups: 30% and 12%. The figures were rounded off to 81. A consecutive sampling technique was used to collect the sample, and the patients were allocated into three groups by lottery method: Group-L for Lidocaine, Group-S for salbutamol, and Group-BS for beclomethasone plus salbutamol (Clenil compositum). The lottery method involved preparing sealed envelopes for each enrolled patient, with the assigned group (L, S, or BS) written inside. Patients were then randomly assigned to a group by drawing one envelope, ensuring unbiased allocation. All the patients admitted to the ICU, aged between 18-70 years, with a diagnosis of mild to moderate ARDS, having a history of COVID-19, presenting with complaints of cough, hypoxia, and respiratory distress, and receiving non-invasive ventilation were included in the study. ARDS was classified as per Berlin's criteria; Mild ARDS: PaO_2/FiO_2 >200 mmHg & moderate ARDS: $\leq$200 mmHg, with a PEEP $\geq$5cmH_2O. The patients with pre-existing chronic respiratory illnesses, already on steroids or bronchodilators, were excluded from the study.

For nebulization, a total of 4 mL aerosol volume was achieved by mixing the under-study drug in 2 mL of sterile Saline. For the Group-L 1 mg/kg lidocaine plane (2 mL approximately), for Group-S 0.5% salbutamol 2mL (5 mg/mL salbutamol sulphate solution), and for Group-BS 2 mL of Clenil compositum (beclomethasone 0.8mg ± salbutamol 16mg) was used. Nebulization was done through the separate nebulizing port available in the Drager ventilator while patients were on the non-invasive ventilatory mode, i.e., high flow oxygen (HFO) mode, and some patients were on CPAP mode available in the ventilator. Every patient was nebulized for 10 minutes at least per treatment, four times a day. Both the operator and patients were blinded to these drugs.

Our primary outcome was the efficacy of drugs, i.e., improvement in hypoxia, reduction in respiratory distress, and successful cough suppression. While the secondary outcome was the safety profile of the drugs, minimal complications like tachycardia, tremors, arrhythmias, dizziness, and agitation. Improvement in hypoxia was assessed by a rise of 10% in PaO_2 and/or SpO_2 from the baseline, and improvement in respiratory distress was noted by > 10% amelioration in the respiratory rate. Cough severity was assessed on the 'cough severity scale'; a subjective score, from '0-no cough' to '4-severe, strenuous cough, accompanied by chest discomfort[23]. Cough suppression was considered successful at a score between 0-1 and failed with a score $\geq$2.

Table 1: Demographic and clinical data, and outcome variables

Parameters		Total (n = 81)	Groups			P-value
			Lidocaine (n = 27)	Salbutamol (n = 27)	Beclomethasone ± Salbutamol (n = 27)	
Gender	Male	55 (68)	19 (70)	17 (63)	19 (70)	0.797
	Female	26 (32)	8 (30)	10(37)	8 (30)	
* Age (years)		60.73 ± 14	55 ± 15	64 ± 14	63 ± 11	0.039
* Baseline SpO_2		0.827 ± 0.07	0.84 ± 0.07	0.815 ± 0.07	0.823 ± 0.08	0.428
* P/F Ratio(mmHg)		206.8 ± 18	210 ± 18	204 ± 17	206 ± 19	0.428
ARDS	Mild	52 (64.2)	18 (66)	16 (59)	18 (66)	0.807
	Moderate	29 (35.8)	09 (34)	11 (41)	09 (34)	
PaO_2 (mmHg)	Before nebulizing	55 ± 7.8	56 ± 7.7	54 ± 8	55 ± 7.8	0.725
	After nebulizing	70 ± 18.6	81.4 ± 22	63.3 ± 12.4	65.8 ± 14.8	0.001
% Improvement in PaO_2		19%	28.6%	13.3%	15%	0.001
Resp. rate Improvement	>10% from baseline	-	24 (89)	16 (59)	15 (55)	0.016
Cough Suppression		46 (56.8)	23 (85)	8 (30)	12 (44)	0.001
Complications		30 (37)	2 (7.4)	15 (55)	13 (48)	0.001

*Data presented as n (%) or mean ± SD; P < 0.05 considered significant; *Post HOC analysis showed no significant difference.*

Every time before and after the nebulization, respiratory rate, PaO_2 and/or SpO_2, heart rate, cough severity score, and cardiac rhythm were recorded on a pre-designed proforma. The demographic details of the patients, along with co-morbidities, the drugs used, their effects on the cough, and any associated complications, were also recorded.

2.1. Statistical analysis

Data were entered in SPSS version 26.0. The categorical variables like gender, effects on cough suppression, cough severity, presence of co-morbidities, tachycardia, tremors, dizziness, and agitation are presented as percentages and frequencies. Numerical variables like age of the patients, heart rate, respiratory rate, PaO_2, SpO_2, and PaO_2/FiO_2 ratio are presented as mean and standard deviation. The Chi-square test is used to compare the categorical variables, while ANOVA is used to compare the numeric variables between the three groups. The paired t-test is used to compare the numeric variables within each group. $P < 0.05$ is considered significant.

3. RESULTS

Data of 81 patients (27 in each group) were obtained, including 68% males and 33% females with a mean age of 60 years, PaO_2 55 ± 7.8 mmHg, and a mean P/F ratio of 206 mmHg at admission. There were no statistically significant differences found regarding gender, baseline PaO_2, SpO_2, P/F ratio, and severity of ARDS between the three groups (Table 1). A total of 36% of the patients presented with severe ARDS in the ICU.

Regarding primary outcomes (Table 1), improvement in hypoxia, as indicated by a mean rise in PaO_2 from the baseline, was more profound in the Group-L (28.6%) as compared to Group-S and Group-BS (13.3% vs. 15% respectively), and it was statistically significant (P = 0.001). Cough suppression was effectively obtained in the Group-L than the Group-S and Group-BS (85% vs 30% vs 44% respectively) with a significant p (0.001). Profound improvement in respiratory distress was seen in Group-L as compared to Group-S and Group-BS (89% vs 59% vs 55% respectively), with a significant P = 0.016. Our secondary outcome, complications were minimal in the Group-L, where only 2 patients suffered from dizziness and agitation, as compared to Group-S and Group-BS (7% vs 55% vs 48% respectively) with a P = 0.001 (Table 1). Most of the complications were agitation, tachycardia, and dizziness.

Post hoc analysis was performed to further clarify the differences in outcomes between the groups in a one-to-

Table 2: Post HOC analysis for PaO_2 between the groups

Variables	Groups		P-value
Post PaO_2	Lidocaine (L)	S	0.001
		BS	0.002
	Salbutamol (S)	L	0.001
		BS	0.913
	Beclomethasone + Salbutamol (BS)	L	0.002
		S	0.913
Percentage Improvement PaO_2	Lidocaine (L)	S	0.001
		BS	0.001
	Salbutamol (S)	L	0.001
		BS	0.726
	Beclomethasone + Salbutamol (BS)	L	0.001
		S	0.726

P < 0.05 is considered significant

one manner (Table 2). It is obvious from the table that there were no statistically significant differences found between Group-S and Group-BS regarding improvement in hypoxia, with P = 0.913. But the difference of outcome was statistically significant between the Group-L & Group-S (P = 0.001), and Group-L & Group-BS (P = 0.002).

When compared within each group (Table 3), hypoxia shows significant improvement after nebulization. In Group-L, there is a mean rise in PaO_2 from baseline 56 to 81 mmHg, in Group-S from 54 to 63.3 mmHg, and in Group-BS from 55 to 65.8 mmHg, with a significant P (0.001).

4. DISCUSSION

We conducted this study to assess the role of lidocaine, comparing its efficacy with the conventional drugs in patients having post-COVID ARDS and symptoms of cough, hypoxia, and respiratory distress on non-invasive ventilation in the ICU. Our results are quite convincing regarding the effectiveness of lidocaine in the improvement of hypoxia, respiratory distress, and cough suppression. Its effects are not only comparable to the conventional drugs but also superior to them, with minimal complications. To our understanding, lidocaine works both ways: direct and indirect. Directly, it improves hypoxia and respiratory distress by reducing respiratory tract inflammation due to its anti-inflammatory properties. And indirectly, it can improve hypoxia and respiratory distress by effectively suppressing the cough.

Lidocaine has a broad clinical spectrum. Its pharmacodynamics, pharmacokinetics, and anti-inflammatory properties are revealed in previous studies.[19] Nebulized lidocaine exerts rapid topical anesthetic and anti-inflammatory effects on the airway mucosa, which were observable within the short nebulization and post-nebulization period due to its quick onset of action. We observed its contribution to symptom amelioration and improved respiratory mechanics in our study. Lan et al. (2005) and Azuma et al. (2000) have described in detail that local anesthetics impede the activity of integrins and leukocyte adhesion molecule-1, causing inhibition of adhesion of leukocytes to the endothelium, thus preventing the endothelial damage. This will consequently withhold leaky vasculature and ultimately prevent pulmonary edema and hypoxia.[24,25]

A study by Lahav et al. (2002), has clearly described the role of local anesthetics in the reduction of the inflammatory process.[26] They reported that local anesthetics have inhibitory effects on the secretions of inflammatory markers (IL-8 and IL-1b), and simultaneously boost the secretions of an anti-inflammatory molecule (IL-1).

Another study has confirmed the inhibitory effects of inhaled lidocaine on GATA3 (GATA-binding protein 3

Table 3: Improvement in PaO2within the groups before and after nebulization

Drug groups	PaO_2	Mean ± SD (mmHg)	95% CI of diff.		*P-value
			Lower	Upper	
Lidocaine	Before	56 ± 7.7	-31.45	-19.433	0.001
	After	81.4 ± 22			
Salbutamol	Before	54 ± 8	-12.259	- 6.18	0.001
	After	63.3 ± 12.4			
Beclomethasone ± Salbutamol	Before	55 ± 7.8	-14.13	-7.499	0.001
	After	65.8 ± 14.8			

**P value obtained using the Paired T test; P < 0.05 is considered significant*

to DNA sequence [A/T]GATA[A/G]) expression and pro-inflammatory cytokines and chemokines, thus preventing the peri-bronchial fibrosis and mucus production in asthma.[27] These are some evidence-based fine explanations of the anti-inflammatory effects of lidocaine in the scenario of CRS, which fits well with our research results.

Going through the literature search, we found a few studies regarding lidocaine utilization in cough suppression and respiratory distress. Banihashem et al. (2015) studied ninety female patients undergoing general anesthesia.[28] They compared the effects of beclomethasone and lidocaine sprays for cough and sore throat after endotracheal intubation. Their results indicated a lower incidence of post-extubation cough and sore throat with lidocaine usage, and are in accordance with our study results.

An extensive literature review, conducted by Slaton et al. (2013) has outlined the effectiveness of nebulized lidocaine in uncontrolled cough and asthma where the conventional treatment failed. They also referred to the studies in which the use of lidocaine as a steroid-sparing drug was evident when used in the long-term treatment for asthma. Their data support our study outcomes.[29]

Honarmand et al. (2008) compared the inhaled beclomethasone with intravenous lidocaine in 120 patients undergoing endotracheal intubations for elective surgery.[30] And they found that beclomethasone and lidocaine are comparable in decreasing cough and postoperative sore throat. Again, these findings are consistent with our results.

Other researchers conducted randomized trials to assess the efficacy of β2-agonists in the treatment of ARDS.[31,32] As per their results, it was found that beta-agonists have no clinical benefits, and they were associated with poor outcomes. This finding in both trials supports our research results, where nebulized salbutamol was found to have more complications than lidocaine. The combination of salbutamol with beclomethasone for nebulization was also not very convincing because of unfavorable outcomes associated with their use.

5. CONCLUSION

Lidocaine is found to be more effective than salbutamol and the combination of beclomethasone + salbutamol in the improvement of hypoxia, respiratory distress, and cough suppression with minimal hazardous effects, in post-COVID ARDS. ARDS is a complex syndrome with multiple severe symptoms requiring multi-drug therapy. Lidocaine is not a remedy for all the symptoms of ARDS, but its contribution towards improvement in some serious symptoms like respiratory distress and hypoxia is undeniable. If only these can be under control, the burden on the ICU will be decreased and hence the mortality.

6. LIMITATIONS

There are some limitations to this study, like the sample being small. More trials with a larger sample size are required in the future, including the effects of drugs on the plasma levels of inflammation markers in patients with post-COVID ARDS.

7. Data availability

The numerical data generated during this research are available from the authors.

8. Conflict of interest

All authors declare that there was no conflict of interest.

9. Funding

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

All authors contributed to the concept, conduct of the study, data accumulation, and manuscript drafting.

All authors have approved the final draft.

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