# Supplemental Material

Comparison of Mechanical Insufflation-Exsufflation and Hypertonic Saline with Hyaluronic Acid with Conventional Open Catheter Suctioning in Intubated Patients.

Miguel Sánchez-García, Manuel Álvarez-González, Sara Domingo-Marín, Ángela del Pino-Ramírez, Fernando Martínez-Sagasti, Paloma González-Arenas, Carlos Cardenal-Sánchez, Elena Velasco-López, Antonio Núñez-Reiz

**Contents**

[Supplemental Material 1](#_Toc150369195)

[e-Figure 1. Schematic representation of the respiratory secretion suctioning procedures in the four study groups. 3](#_Toc150369196)

[e-Table 1. Baseline characteristics at ICU admission and at study inclusion. 6](#_Toc150369197)

[e-Table 2. Mean bispectral index 9](#_Toc150369198)

[e-Table 3. Mean Heart rates per study group and time points. 11](#_Toc150369199)

[e-Table 4. Mean Blood Pressures per study group and time points 13](#_Toc150369200)

[e-Table 5. Mean noradrenaline infusion rates (microgram/kg) per group and time points. 15](#_Toc150369201)

[e-Table 6. Ventilation modes (a), PEEP (b) and compliance (c) 17](#_Toc150369202)

[e-Table 7. Blood pH (a), pCO2 (b) and PaO2/FiO2 ratio (c) 22](#_Toc150369203)

## e-Figure 1. Schematic representation of the respiratory secretion suctioning procedures in the four study groups.



HS-HA denotes 7% hypertonic saline with 0,1% hyaluronic acid and MI-E mechanical insufflation-exsufflation.

1) Before the study intervention. 2) During the respective study interventions. Subjects were disconnected from the ventilator tubing and reconnected and returned to their baseline ventilation status after the study interventions.

A. Group 1. Conventional sterile catheter open suctioning according to local protocol at -120 to -150 mBar.

B. Group 2. Conventional catheter open suctioning after nebulization of 5 mL of HS-HA by a ventilator-integrated jet nebulization system synchronised with inspiration and placed at the Y-connector in the inspiratory limb of the ventilator tubing.

C. Group 3. A bacterial heat-moisture exchange filter was placed at the airway clearance device output and connected to the artificial airway through a single limb corrugated tubing (green striped arrow). Humidified O2 at 6 L/min was applied to the Luer port of the bacterial filter. 10 to 15 cycles of MI-E at 50 cmH20 insufflation pressure with an inhale time of 4 seconds and -50 cmH20 exsufflation pressure with exhale time 3 seconds were applied and repeated after 1-2 minutes if productive. High-frequency 16 Hz oscillation during both insufflation and exsufflation plateaus and patient-triggered “cough track” mode with high inhale flow were used. In patients not triggering the MI-E cycle, the device was set to mandatory cycling with a 2-second pause. Study subjects were not instructed to exhale or cough during the exsufflation phase.

D. Group 4. MI-E was performed as in C (Group 3) with added simultaneous nebulization of HS-HA. Humidified O2 at 6 L/min was not provided through the bacterial filter but through the jet nebulizer (Tubing to jet nebulizer in grey striped arrows). The jet nebulizer was connected to a T-tube inserted in the corrugated tubing at 15-20 cm from the airway clearance device (grey tubing from filter to nebulizer; green tubing from nebulizer to endotracheal tube or tracheostomy cannula).

e-Table 1. Baseline characteristics at ICU admission and at study inclusion.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Catheter open suctioningN=30 | Catheter open suctioning + HS-HAN=30 | MI-EN=30 | MI-E + HS-HAN=30 | p value |
| Blood gases at inclusion, mean ± SD |  |  |  |  |  |
| Arterial pH | 7.39 ± 0.07 | 7.41 ± 0.09 | 7.42 ± 0.06 | 7.39 ± 0.07 | 0.33 |
| PaCO2 | 43.4 ± 8.1 | 40.2 ± 7.1 | 42.2 ± 6.8 | 42.8 ± 6.0 | 0.42 |
| Venous pH | 7.38 ± 0.02 | 7.35 ± 0.06 | 7.38 ± 0.05 | 7.41 ± 0.04 | 0.078 |
| PvCO2 | 48.4 ± 10.6 | 51.4 ± 14.1 | 48.7 ± 3.9 | 49.3 ± 8.5 | 0.95 |
| Ventilation modes, n (%) |  |  |  |  | 0.26 |
| Mechanically assisted ventilation | 17 (56.7) | 19 (63.3) | 22 (73.3) | 25 (83.3) |  |
| CPAP | 3 (10) | 2 (6.7) | 0 | 1 (3.3) |  |
| Spontaneous ventilation | 10 (33.3) | 9 (30) | 8 (26.7) | 4 (13.3) |  |
| Ventilator settings and mechanics |  |  |  |  |  |
| Minute ventilation, median (IQR) | 9.8 (7.9; 11.85) | 9.5 (8.2; 11.1) | 8.3 (7.0; 10.5) | 8.4 (7.8; 12.1) | 0.31 |
| Tidal volume, median (IQR) | 503 (415; 575) | 549 (484; 630) | 490.5 (436; 532) | 500 (471; 601) | 0.13 |
| Total breaths/minute, median (IQR) | 18 (16; 24) | 18 (16; 20.2) | 18 (15; 22) | 18 (14; 22) | 0.63 |
| PaO2/FiO2, mean ± SD | 264.4 ± 111 | 236.7 ± 126 | 244.1 ± 111 | 253.4 ± 67 | 0.94 |
| PEEP, median (IQR) | 7.5 (5; 8) | 7 (5.75; 8) | 6 (5; 8) | 6 (5; 8) | 0.63 |
| Peak pressure, mean ± SD | 21.9 ± 5.2 | 22.5±5 | 20.6±8.3 | 22.3±4.2 | 0.87 |
| Plateau pressure, mean ± SD | 20.8 ± 4.8 | 20.9±5 | 19.6±8.6 | 20.3±5.1 | 0.84 |
| Cst, median (IQR) | 39.33 (25.3; 53) | 45.4 (28.3; 53) | 34.1 (27.6; 56) | 40 (31.4; 50.1) | 0.84 |
| Cdin, median (IQR) | 37.9 (23.4; 50) | 35.4 (26.7; 50.1) | 33.7 (26.8; 42.6) | 35.7 (26.7; 45.9) | 0.98 |
| Sat O2 (%), median (IQR) | 98 (96; 99) | 97 (96; 98.5) | 96.5 (95; 99) | 98.6 (97; 99) | 0.13 |
| Noradrenaline infusion, n (%)dose, median (IQR) µg/kg/min | 17 (56.7) 0.09 (0; 0.4) | 18 (60) 0.12 (0; 0.48) | 15 (50) 0.04 (0; 0.38) | 14 (46.7) 0 (0; 0.31) | 0.720.74 |
| Blood pressure, mmHg, mean ± SD | 77.5 ± 11.2 | 81.5 ± 12.9 | 79.1 ± 17.7 | 81.5 ± 13.8 | 0.62 |
| Heart rate, beats per minute, mean ± SD | 89.6 ± 19.4 | 83 ± 19.5 | 84.5 ± 16.7 | 80.4 ± 18.3 | 0.28 |
| Hypovolemia, n (%) | 8 (26.7) | 2 (6.9) | 9 (30) | 4 (13.3) | 0.79 |
| Temperature (Celsius), median (IQR) | 37.3 (36.8; 37.6) | 37 (36.4; 37.2) | 36.9 (36.5; 37.4) | 36.8 (36.5; 37.1) | 0.013 |
| IV sedation ± analgesia, n (%) | 23 (76.7) | 21 (70) | 25 (83.3) | 26 (86.7) | 0.39 |
| Midazolam dose, median (IQR) | 0 (0; 0.13) | 0 (0; 0) | 0 (0; 0.54) | 0 (0; 0.14) | 0.073 |
| Propofol dose, median (IQR) | 70 (0; 200) | 150 (95; 240) | 10 (0; 190) | 60 (0; 160) | 0.067 |
| Remifentanil dose, median (IQR) | 0 (0; 0) | 0 (0; 0) | 0 (0; 0) | 0 (0; 0) | 0.48 |
| Fentanyl dose, median (IQR) | 0.012 (0.0003; 1.02) | 0.012 (0.004; 0.032) | 0.014 (0.0004; 0.037) | 0.002 (0.0004; 0.02) | 0.71 |
| IQR, interquartile range; HS-HA, 7% hypertonic saline with hyaluronic acid; MI-E, mechanical insufflation-exsufflation; Cst, static lung compliance; Cdin, dynamic lung compliance. |

## e-Table 2. Mean bispectral index

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** **group** | **Timepoints** | **n** | **Mean percentage (95%CI)** |
| Catheter open suctioning | Baseline | 3 | 39.7 (23.5 to 55.8) |
| During RSS | 3 | 39.7 (23.5 to 55.8) |
| 5-minute | 3 | 61.3 (16.9 to 100) |
| 60-minute | 3 | 40.7 (16.2 to 65.2) |
| Catheter open suctioning + HS-HA | Baseline | 7 | 39.1 (32.5 to 45.8) |
| During RSS | 7 | 39.1 (32.5 to 45.8) |
| 5-minute | 7 | 53 (35.3 to 70.7) |
| 60-minute | 7 | 48.7 (35.5 to 61.9) |
| MI-E | Baseline | 6 | 55.7 (37.6 to 73.7) |
| During RSS | 6 | 55.7 (37.6 to 73.7) |
| 5-minute | 6 | 61.8 (43 to 77.7) |
| 60-minute | 6 | 61.2 (40.2 to 82.1) |
| MI-E + HS-HA | Baseline | 5 | 43.8 (21.4 to 66.2 |
| During RSS | 5 | 43.8 (21.4 to 66.2) |
| 5-minute | 5 | 53.6 (19.8 to 87.4) |
| 60-minute | 5 | 45.8 (20 to 71.5) |
| MI-E mechanical insufflation-exsufflation. HS-HA 7% hypertonic saline-0.1% hyaluronic acid. CI confidence interval |

## e-Table 3. Mean Heart rates per study group and time points.

|  |  |  |
| --- | --- | --- |
| **Time point** | **Group** | **Mean (95%CI)** |
| Baseline | 1 | 89.6 (82.4 to 96.8) |
|  | 2 | 83.0 (75.7 to 90.3) |
|  | 3 | 84.5 (78.3 to 90.8) |
|  | 4 | 80.4 (73.6 to 87.3) |
|  | Total | 84.4 (81 to 87.7) |
| 5-minute | 1 | 90.3 (83.5 to 97.1) |
|  | 2 | 82.6 (75.5 to 89.8) |
|  | 3 | 84.7 (78.5 to 91) |
|  | 4 | 83.1 (76.1 to 90.1) |
|  | Total | 85.2 (81.9 to 88.5) |
| 60-minute | 1 | 88.5 (82 to 94.9)  |
|  | 2 | 81.9 (75.5 to 88.4) |
|  | 3 | 84.7 (79 to 90.4) |
|  | 4 | 81.9 (74.6 to 89.2) |
|  | Total | 84.2 (81.1 to 87.4) |
| CI confidence interval |

## e-Table 4. Mean Blood Pressures per study group and time points

|  |  |  |
| --- | --- | --- |
| **Time point** | **Group** | **Mean (95%CI)** |
| Baseline | 1 | 77.5 (73.3 to 81.7) |
|  | 2 | 81.5 (76.7 to 86.4) |
|  | 3 | 79.1 (72.5 to 85.7) |
|  | 4 | 81.5 (76.3 to 86.6) |
|  | Total | 79.9 (77.4 to 82.4) |
| 5-minute | 1 | 78.4 (74.2 to 82.6) |
|  | 2 | 83.4 (78.6 to 88.3) |
|  | 3 | 78.3 (71.6 to 84.9) |
|  | 4 | 84.1 (73.3 to 94.9) |
|  | Total | 81.0 (77.6 to 84.5) |
| 60-minute | 1 | 78.1 (73.1 to 83.1) |
|  | 2 | 80.6 (76.2 to 85) |
|  | 3 | 77.6 (71.8 to 83.4) |
|  | 4 | 78.5 (72.9 to 84.1) |
|  | Total | 78.7 (76.2 to 81.2) |

## e-Table 5. Mean noradrenaline infusion rates (microgram/kg) per group and time points.

|  |  |  |
| --- | --- | --- |
| **Time point** | **Group** | **Mean (95%CI)** |
| Baseline | 1 | 0.30 (0 to 3.33) |
|  | 2 | 0.43 (0 to 5.55) |
|  | 3 | 0.21 (0 to 1.23) |
|  | 4 | 0.24 (0 to 2.31) |
|  | Total | 0.30 (0 to 5.55) |
| 5-minute | 1 | 0.30 (0 to 3.33) |
|  | 2 | 0.43 (0 to 5.55) |
|  | 3 | 0.22 (0 to 1.23) |
|  | 4 | 0.23 (0 to 2.31) |
|  | Total | 0.30 (0 to 5.55) |
| 60-minute | 1 | 0.24 (0 to 1.66) |
|  | 2 | 0.41 (0 to 5.55) |
|  | 3 | 0.22 (0 to 1.23) |
|  | 4 | 0.21 (0 to 1.73) |
|  | Total | 0.27 (0 to 5.55) |
| CI confidence interval |

## e-Table 6. Ventilation modes (a), PEEP (b) and compliance (c)

1. **Ventilation modes (n) per study group per timepoint.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Timepoints** | **Ventilation mode** | **Study group 1** | **Study group 2** | **Study group 3** | **Study group 4** |
| Baseline | Spontaneous | 10 | 9 | 8 | 4 |
| CPAP | 3 | 2 | 0 | 1 |
| MV | 17 | 19 | 22 | 25 |
| At 5 minutes | Spontaneous | 12 | 9 | 8 | 5 |
| CPAP | 1 | 1 | 0 | 0 |
| MV | 17 | 20 | 22 | 25 |
| At 60 minutes | Spontaneous | 11 | 9 | 7 | 6 |
| CPAP | 1 | 2 | 0 | 1 |
| MV | 18 | 19 | 23 | 23 |
| Ventilation mode distribution was balanced between study groups and across timepoints (p=0.25) |

1. **Positive end-expiratory pressure (cmH2O) per study group per timepoint**

|  |  |  |
| --- | --- | --- |
| **Study Group** | **Time point** | **Median (IQR)** |
| Catheter open suctioning | Baseline | 7 (5; 8.25) |
| 5-minute | 7 (5; 8.5) |
| 60-minute | 7 (5; 8.5) |
| Catheter open suctioning + HS-HA | Baseline | 7 (5; 8) |
| 5-minute | 7 (5.75; 8) |
| 60-minute | 7 (7.75; 8) |
| MI-E | Baseline | 8 (6; 8.5) |
| 5-minute | 6 (5; 8) |
| 60-minute | 7 (5; 8) |
| MI-E + HS-HA | Baseline | 7 (5; 8) |
| 5-minute | 6 (5; 8) |
| 60-minute | 6 (5; 8) |

1. **Median (IQR) Lung compliance per timepoint in each study group**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Timepoints** | **Compliance** | **Study group 1** | **Study group 2** | **Study group 3** | **Study group 4** | **P value** |
| Baseline | Dynamic | 33.5 (23.5; 50.8) | 33.9 (25.5; 41.9) | 40.1 (31.9; 49.9) | 38.5 (25.1; 50.1) | 0.44 |
| Static | 36.6 (27.3; 53.5) | 38.3 (28.9; 49.2) | 41.5 (33.6; 49.9) | 39.7 (29.8; 54) | 0.61 |
| At 5 minutes | Dynamic | 35.2 (24.4; 49.8) | 33.9 (26.2; 51.9) | 36.4 (29.4; 42.9) | 35.2 (26.2; 44) | 0.92 |
| Static | 35.8 (27.9; 55.5) | 42.3 (30.2; 55.7) | 38.8 (32.4; 51.4) | 42.4 (33.3; 56.1) | 0.93 |
| At 60 minutes | Dynamic | 34.8 (25.3; 51.4) | 37.4 (25.1; 54.2) | 32 (27.8; 40.5) | 33.7 (24.9; 43.5) | 0.88 |
| Static | 36.5 (30; 51.4) | 42.4 (29.1; 53.8) | 38.1 (28.4; 52.4) | 41.8 (31; 53.9) | 0.94 |
|  |

## e-Table 7. Blood pH (a), pCO2 (b) and PaO2/FiO2 ratio (c)

1. **Arterial pH per timepoint in each study group**

|  |  |  |
| --- | --- | --- |
| **Study Group** | **Time point** | **Mean (95%CI)** |
| Catheter open suctioning | Baseline | 7.4 (7.36 to 7.4) |
| 5-minute | 7.40 (7.36 to7.43) |
| 60-minute | 7.41 (7.37 to 7.44) |
| Catheter open suctioning + HS-HA | Baseline | 7.41 (7.36 to 7.45) |
| 5-minute | 7.41 (7.38 to 7.44) |
| 60-minute | 7.41 (7.38 to 7.44) |
| MI-E | Baseline | 7.42 (7.4 to 7.45) |
| 5-minute | 7.40 (7.35 to 7.44) |
| 60-minute | 7.40 (7.35 to 7.44) |
| MI-E + HS-HA | Baseline | 7.41 (7.4 to7.44) |
| 5-minute | 7.44 (7.41 to 7.5) |
| 60-minute | 7.44 (7.42 to 7.47) |
| CI confidence interval |

1. **Arterial pCO2 per timepoint in each study group**

|  |  |  |
| --- | --- | --- |
| **Study Group** | **Time point** | **Mean (95%CI)** |
| Catheter open suctioning | Baseline | 44.2 (39 to 49.5) |
| 5-minute | 40.9 (37 to 44.8) |
| 60-minute | 40.7 (36.7 to 44.7) |
| Catheter open suctioning + HS-HA | Baseline | 40.3 (36.6 to 44.1) |
| 5-minute | 42.3 (38.7 to 46) |
| 60-minute | 42.1 (39.2 to 44.9) |
| MI-E | Baseline | 42 (38.7 to 45.4) |
| 5-minute | 43.1 (39.2 to 47) |
| 60-minute | 43.1 (37.4 to 46.4) |
| MI-E + HS-HA | Baseline | 43.1 (39.6 to 46.5) |
| 5-minute | 40.1 (36.7 to 44.7) |
| 60-minute | 39.4 (37.4 to 41.5) |
| CI confidence interval |

1. **Mean PaO2/FiO2 ratio per timepoint (c. 1) and per study group (c .2).**

**c. 1**

|  |  |
| --- | --- |
| **Timepoints** | **Mean (95%CI)** |
| Baseline | 270.8 (253.5 to 288) |
| 5-minutes | 259.5 (241.6 to 277.4) |
| 60-minutes | 270.1 (252.9 to 287.3) |

**c. 2**

|  |  |  |
| --- | --- | --- |
| **Study group** | **Timepoints** | **Mean (95%CI)** |
| Catheter open suctioning | Baseline | 273.5 (239.8 to 307.2 |
| 5-minute | 251.0 (216 to 286 |
| 60-minute | 257.6 (224 - 291.2) |
| Catheter open suctioning + HS-HA | Baseline | 290.2 (255.3 to 325.1) |
| 5-minute | 269.2 (232.9 to 305.4 |
| 60-minute | 271.2 (236.5 to 306) |
| MI-E | Baseline | 252.1 (218.4 to 285.8) |
| 5-minute | 249.1 (214.1 to 284.1) |
| 60-minute | 278.2 (244.6 to 311.8) |
| MI-E + HS-HA | Baseline | 267.2 (231.7 to 302.7) |
| 5-minute | 268.8 (231.9 to 305.7) |
| 60-minute | 273.3 (237.9 to 308.8) |