

Aggregated n-of-1 randomised controlled trial of nebulized fentanyl or nebulized furosemide in palliative care patients with refractory breathlessness.

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Background: Advance cancer patients frequently have breathlessness and worsening by refractory to conventional therapies, which need adjunctive therapy. Nebulized Fentanyl and nebulized furosemide have been identified as a novel symptoms approach. Individual patients with the same breathlessness conditions may respond differently to similar treatments, thus no standard adjunctive treatments. N-of -1 study is a within-patient randomized, double-blind, and crossover trials in 1 patient; in each patient act as his own controls, and provides the most rigorous information for individual patient. This study aims to comparing the efficacy in relief breathlessness of fentanyl, furosemide and sterile water.

Methods: N-of-1 study which enrolled patients at Ramathibodi hospital who have breathlessness with mMRC scored ≥ 3 from 1st Jan 2019 to 31st Jan 2020. Study was done as 1 cycle of 3-days of treatment that nebulized fentanyl or furosemide or sterile water (SW). Fentanyl 50 mcg or Furosemide 40 mg or SW that all diluted in SW to be in 6 ml. Jet nebulizer increased delivery of aerosol to lungs that all administered for 4 minutes. Main outcome measured breathlessness intensity Borg scale: 0-10, peripheral capillary O₂ saturation, Visual cough score, satisfactions, and adverse events (AEs) that collected at baseline, 15, 30- and 60-minutes post treatment. Type of medication that patients preferred.

Results: 19 patients were enrolled; 68.4% were ECOG status 4. All patient previously treated with systemic opioids with dose 29.8 ± 20.9 (0-72) mg/day. Majority were diagnosed with lung metastatic cancer. Baseline of mean Borg scale were not significant in all groups; Fentanyl 6.73 ± 0.93 ; Furosemide 6.47 ± 1.34 ; Sterile water 6.57 ± 1.34 respectively. All 3 medications significantly reduced Borg scale over time; Fentanyl -2.84 ± 0.17 (95% CI -3.19 to -2.49); $p=0.0001$, Furosemide -3.05 ± 0.22 (95% CI -3.49 to -2.61); $p=0.0001$, and Sterile water -2.52 ± 0.21 (95% CI -2.95 to -2.10); $p=0.0001$. There were no significantly different in reduction of breathlessness, AEs and change in visual cough score in all medications. Most of AEs were mild grade. Majority of patient preference was furosemide (42.0%).

Conclusions: Adjunctive treatment ultrasonic nebulizer drugs with fentanyl, furosemide and sterile water significantly improve breathlessness symptoms. In addition, the result may be from the use of ultrasonic nebulization which is another factor. No significant different in efficacy, adverse events in nebulized fentanyl, furosemide and sterile water. N-of-1 trials may provide a rational and effective method to best choose drugs for individuals with breathlessness.