Nebulized Versus IV Amikacin as Adjunctive Antibiotic for Hospital and Ventilator-Acquired Pneumonia Postcardiac Surgeries: A Randomized Controlled Trial

BACKGROUND:

- Nosocomial pneumonia has high mortality rates and is of great concern in patients who have just undergone cardiac surgery. Aminoglycosides are very effective at treating pneumonia when in combination with other antibiotics, but can be nephrotoxic.
- Nebulized aminoglycosides were used in the past to enhance efficacy and reduce nephrotoxicity, but increased resistance to aminoglycosides decreased their usage.

OBJECTIVE:

- To determine the efficacy and safety of nebulized amikacin compared to IV amikacin in patients with nosocomial pneumonia with resistant gram negative bacteria.

METHODS

- **Design:** Single site, unblinded, randomized parallel trial; Duration: One year
- **Inclusion Criteria:** 21-65 yo, consciousness level on Glasgow scale between 4 and 15, positive MDR-GNB susceptible to amikacin, clinical suspicion of HAP
- **Exclusion Criteria:** allergy to sulfite in amikacin, multiorgan dysfunction or psychiatric illness, not tolerant to nebulized amikacin, pregnant, lactating, baseline CrCl less than 30 mL/min, or indicated for monotherapy
- **Primary Outcome:** Clinical cure on day 7 of amikacin initiation.
- **Secondary Outcomes:** Length of hospital stay, length of ICU stay, days on amikacin, days on mechanical ventilation (MV), MV free days, clinical cure with each bacterial isolate, mortality rate, and nephrotoxicity.
- 133 patients were randomized: 86 patients received 400 mg of nebulized amikacin twice daily and 47 patients received IV amikacin at 20 mg/kg once daily. All participants received IV Zosyn of an unknown strength.
- Power 80% with an alpha equal to 0.05 and achieving a 16% difference in clinical cure required 88 patients. Actual power was reported as 83% with 133 patients for the primary outcome in the study.
- Data handling method was intent-to-treat

RESULTS

- 82 patients in the nebulizer arm and 41 patients in the IV arm completed the study, but all 133 were included in the intent-to-treat analysis.
- **Primary Outcome Measures:** There was a statistically significant difference in cure rate between the nebulized arm (91.8%) and the IV arm (70.2%; p=0.002).
- **Secondary Outcome Measures:** The following secondary outcomes were statistically significant (nebulizer arm, IV arm; p value): length of ICU stay (6 days, 9 days; p=0.010), days on amikacin (7 days, 8 days; p=0.022), duration on MV (3 days, 7 days; p=0.035), and signs of nephrotoxicity. The included measures for nephrotoxicity were as follows: SCr after 48 hours of administration (1 mg/dL, 1.2 mg/dL; p=0.043), SCr on last day of treatment (1.3 mg/dL, 1.4 mg/dL; p=0.013), CrCl after 48 hours of administration

(80 mL/min, 62 mL/min; p=0.001), and CrCl on last day of treatment (80 mL/min, 70 mL/min; p=0.004).

- **Author's Conclusion:** Nebulized amikacin was associated with a shorter time to clinical cure and shorter stay in the ICU. The nebulized amikacin was also found to be less nephrotoxic than the IV amikacin.

STRENGTHS

- Inclusion and exclusion criteria followed guidelines for use of aminoglycosides, allowing extrapolation to the population that amikacin would be used in.
- Compared the efficacy of the nebulized amikacin to the strongest recommended IV dosage of amikacin.

LIMITATIONS

- Utilized sputum cultures instead of bronchoalveolar lavage to identify bacteria in the lungs.
- Unblinded
- Could not report MIC of pathogens and lung concentrations of amikacin
- Nonventilated patients received nebulized amikacin on inhalation and exhalation
- Patients in nebulizer group had an infection more susceptible to Zosyn
- Patients in IV group had higher than recommended trough levels of amikacin
- Higher percentage of patients in IV group had VAP

CONCLUSIONS

- The study concluded that nebulized amikacin is more effective and less nephrotoxic than the IV amikacin regimen, but the limitations of the study restrict the utility of these results. The study used an appropriate beginning treatment regimen to compare efficacy and safety, but did not appropriately adjust the regimen to ensure proper therapeutic levels throughout the entire study. More studies should be conducted to ensure the safety and efficacy of the medication before implementing any changes to practice.
- Future research:
    - Future studies should be double-blind and double-dummy to help prevent concerns of bias. A range of the nebulized amikacin should be tested against the normalized IV dosage to find safety and efficacy across a dosing range. Studies should also better follow guidelines for dosing and dosing adjustments in IV amikacin. Future studies should include a larger sample size and stratified randomization to ensure similarities between the control and treatment groups.

Reference: Hassan NA, Awdallah FF, Abbassi MM, Sabry NA. Nebulized Versus IV Amikacin as Adjunctive Antibiotic for Hospital and Ventilator-Acquired Pneumonia Postcardiac Surgeries: A Randomized Controlled Trial. Crit Care Med. 2018 Jan;46(1):45-52.

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