DISCUSSION

Ventilator associated pneumonia VAP is a big problem nowadays and its mortality ranged from 24% up to 76%.and VAP is a huge burden on any country's socio economic status and health care facility and in current study we apply the usage of enteral simvastatin 60 mg on mechanically ventilated patients who are suspected to have VAP (new onset fever, leukocytosis, profuse purulent secretion, new chest x-rayfinding as patch or infiltrates) provided that patients stay on mechanical ventilator more than 48 hours.[137]

we applied simvastatin 60 mg enterally versus placebo on 60 mechanically ventilated patients (divided by day by day method of statistical analysis) till 28 days or till discharge from ICU or death. Which came first.[138]

So we followed effect of enteral simvastatin on mortality rate, morbidity (acute respiratory distress syndrome, arrhythmia) ventilator days, vasopressor days and ICU stay length and oxygenation status.also we followed non pulmonary organ failure rate through different laboratory investigations, daily chest x ray imaging for gross chest observation and taking sputum cultures for searching microorganisms.And we followed common side effect of simvastatin as elevated liver enzymes. [139]

In a randomized. Clinical trial placebo controlled double blinded parrel groupmulti center trial performed by L. Papazian et al in France in 26 intensive care units on 250 patients. This study was applied on mechanically ventilated patient for more than 48 hours and have CPIS score ≥5, in this study patient randomized by day by day method of statistic to receive simvastatin 60 mg enterally in the same day of antibiotic therapy addition and given until discharge or death or day 28 which ever occurred first.[140]

This study was stopped due to absolute increase in mortality about 3% in simvastatin group in comparison to control group.[141]

The difference between two studies is that daily routine laboratory investigation requirement and daily calculated SOFA score but in another study SOFA score was calculated in day 3, 7, 14 only and routine laboratory investigation requirement is every other day.[142-143]

Daniel F Mc.Auley et al performed another large multicenter double blinded clinical trial on randomly assigned 540patients with onset of acute respiratory distress syndrome (ARDS) within the previous two days of putting patient on mechanical ventilator to receive 80 mg of enteral simvastatin once daily for maximum 28 days and the primary outcome is to follow number of ventilator days. And secondary outcome was to follow number of free days of ventilator or non pulmonaryorgan failure. [144]

This study found no significant difference between two groups as primary outcome or secondary outcome.as no significant decrease in ventilatordays or significant changes in non pulmonary organ failure rates. And in this study APACHE-II score was applied at admission to ICU and on every other day and this study not depend on CPIS or SOFA scores.[145]

A strong difference between this study and our study in the usage of 80 mg simvastatin versus 60 mg in previous study after two days of invasive mechanical ventilation with no evidence of VAP. Neither clinically nor laboratory or radiologically and the main concern here is HI, and follow up permissive hypercapnea that not affecting hemodynamics of the patients..[146]

In a two centers to arms randomized open label controlled trail done by Demosthenes et al to assess effect of enteral pravastatin 40 mg enterally versus placebo and its effect on frequency of VAP and ICU mortality, this study provide evidence that pravastatin is may favorably affect the outcome of mortality and ICU stay length, but this study have a strong limitations that patient not actually have VAP but more than 48 hours on mechanical ventilator and liable to VAP, and anther limitation is that study not consider neither SOFA nor CPIS scores monitoring and follow up.[147]

So in this study it was said that entral pravastatin used as a prophylactic against VAP not for treatment beside other antibiotic therapy and the aim is to follow VAP appearance and detection, not VAP monitoring and progression.[148]

By a systematic review was conducted of studies which reported effects of atorvastatin treatment in COPD. Data sources searched included reference lists. This study was a mega study and took a large population sample overall 785 citations were identified, from which 21 articles were selected for review.[149-150]

This study was results by Lawes et al in eight papers reporting nine original studies met the selection criteria. One was a randomized controlled trial (RCT), one a retrospective nested case-control study, five were retrospective cohort studies of which one was linked with a case-control study, and one was a retrospective population-based analysis. Outcomes associated with treatment with statins included decreased all-cause mortality in three out of four studies (0.48–0.67 in three studies,0.99 in one study), decreased COPD-related mortality (0.19–0.29), reduction in incidence ofrespiratory-related urgent care (0.74), fewer COPD exacerbations (0.43), fewer intubations for COPD exacerbations (0.1) and attenuated decline in pulmonary function. The RCT reported improvement in exercise capacity and dyspnea after exercise associated withdecreased levels of C-reactive protein and Interleukin-6 in statin users, but no improvement of lung function..[151]

So there is evidence from observational studies and one RCT that atorvastatin may reduce morbidity and/or mortality in COPD patients. Further interventional studies are required to confirm these findings.[152]

But the main limitation of this study is that not all patients were intubated and they have no raising alarm to have VAP.[153-155]

One study was a randomized controlled trial (RCT). The other studies were analyses of observational data and included one case-control study, five historical cohort studies of which one was linked with a case-control study.[156]

Several studies have shown promising results regarding the use of atorvastatin as an adjunctive treatment for sepsis. Most of those studies were retrospective orobservational in nature. The ASEPSIS trial done by Kruger et al and has reportedthat the administration of atorvastatin reduced clinical progression of sepsis but did not improve mortality.[157]

These findings are promising and further multicentertrials are needed to confirm these outcome and to establish whether this class of medications will off erutility in this regard.[158]

Patel and colleagues report the result of a single-center study that randomizedseptic patients to atorvastatin or placebo. The authors found that patients treated with statins had less transition to severe sepsis although mortality was no different between the treated and untreated patients. These findings, although promising, need to be confirmed in larger, multicenter trials.[159]

In this study the main concern is rely on the role of atorvastatin on endothelial cell membrane dysfunction ,and atorvastatin effect on leucocytic response, coagulation cascade and sepsis drivers.[160]

A strong difference between 2 studies that is the main target topic is sepsis in general not particularly VAP and oxygenation status and other chest parameters will not be daily evaluating unless the source of sepsis is chest problem.[161]

In the acute respiratory distress syndrome (ARDS), inflammation in the lungs and other organs can cause life-threatening organ failure.statins can modulate inflammatory responses.studies suggested that statins improved clinical outcomes in patients with sepsis. It is hypothesized that rosuvastatin therapy would improve clinical outcomes in critically ill patients with sepsis-associated ARDS.[162]

A study done by Jonathone and colleagues was conducted it was a multicenter trial in which patients with sepsis-associated ARDS and were randomly assigned to receive either enteral rosuvastatin or placebo in a double blind manner. The primary outcome was mortality before hospital discharge home or until study day 60 if the patient was still in a health care facility. Secondary outcomes included the number of ventilator-free days (days that patients were alive and breathing spontaneously) today 28 and organ-failure–free days to day 14.[163]

The study was stopped because of futility after 745 of an estimated 1000 patients hadbeen enrolled. There was no significant difference between study groups in 60-dayin-hospital mortality.[164]

Rosuvastatin therapy did not improve clinical outcomes in patients with sepsis associated ARDS and may have contributed to hepatic and renal organ dysfunctionand this study is limited to sepsis induced ARDS cases only this was a strong difference on our study.[165]

Retrospective studies have shown that statins decrease the rate and severity of exacerbations, the rate of hospitalization, and mortality in chronic obstructive pulmonary disease (COPD). We prospectively studied the efficacy of simvastatin inpreventing exacerbations in a large, multicenter, randomized trial.[166]

We designed the Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations done by Gerard J. Crineron 885 patients it was performed as a randomized, controlled trial of simvastatin (at a daily dose of 40 mg) versus placebo, with annual exacerbation rates as the primary outcome.[167]

Total of 885 participants with COPD were enrolled for approximately 641 days, an FEV1 that was 41.6±17.7% of the predicted value, and a smoking history of 50.6±27.4 pack-years. At the time of study closeout, the low-density lipoprotein cholesterol levels were lower in the simvastatin-treated patients than in those who received placebo. The mean number of exacerbations per person-year was similar in the simvastatin and placebo groups. The median number of days to the first exacerbation was also similar: 223 days. The number of non fatal serious adverse events per person-year was similar events with simvastatin compared with placebo group. There were 30 deaths in the placebo group and 28 in the simvastatin group.[168]

Simvastatin at a daily dose of 40 mg did not affect exacerbation rates or the time toa first exacerbation in patients with COPD who were at high risk for exacerbations.[169]

This study depends on the pleiotropic effect and anti-inflammatory criteria of simvastatin to decrease chronic airway inflammation and improvement of alveolar membrane stability and decreasing COPD exacerbation severity but majority of patients in this study were not mechanically ventilated and not liable to have VAP and the main outcome was annual exacerbation rate rather than mortality.[170]

RECOMMENDATIONS

1- Routine use of simvastatin not associated with mortality reduction

2- Further study on large population for more evaluation

3- Use of liver support to prevent liver injury .