



# Cisatracurium for acute respiratory distress syndrome: review of current evidence

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## Abstract

### Introduction

Our aim was to review the latest available evidence about whether the use of a continuous infusion of cisatracurium, a neuromuscular blocking agent (NMBA), in patients with acute respiratory distress syndrome (ARDS) had a beneficial effect on clinical outcomes.

### Materials and methods

The following databases were searched: The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 6, 2012), MEDLINE (1950 to June 2012) and EMBASE (1980 to June 2012); the references of relevant trials and review articles identified were also searched. Only randomized controlled trials were included in the meta-analysis. In addition, we have reviewed observational studies in our systematic review. Study selection and extraction of data were all performed independently.

### Results

We included three fully published randomized controlled trials containing 431 patients. The primary outcome of 28-day all-cause mortality was significantly lower in the NMBA group compared with the placebo group (RR 0.68, 95% CI = 0.51–0.92,  $I^2 = 0\%$ ). NMBAs also had a statistically significant effect on ICU mortality (RR = 0.71, 95% CI = 0.55–0.90,

$I^2 = 0\%$ ), overall mortality (RR = 0.73, 95% CI = 0.57–0.92,  $I^2 = 0\%$ ), number of cases of new-onset barotrauma (RR = 0.43, 95% CI = 0.2–0.9,  $I^2 = 0\%$ ) and number of ventilator-free days (MD = 1.91, 95% CI = 0.28–3.55,  $I^2 = 0\%$ ). However, they did not show any significant effect on the duration of mechanical ventilation (RR 1.14, 95% CI = –4.07–6.35,  $I^2 = 0\%$ ) or number of cases of new-onset critical illness neuromyopathy (RR 1.13, 95% CI = 0.76–1.67,  $I^2 = 0\%$ ).

### Conclusion

Our analysis showed that the early, short use of a continuous infusion of cisatracurium led to a statistically significant reduction in mortality in ARDS patients. The potential effects and drawbacks of the intervention were discussed.

### Introduction

Acute respiratory distress syndrome (ARDS) was first described by Ashbaugh in 1967<sup>1</sup> and a global definition was then established by the 1994 American-European Consensus Conference (AECC)<sup>2</sup>. This was recently updated by the Berlin definition<sup>3</sup>, which addressed the limitations of the original AECC classification. ARDS is characterized by bilateral opacities on a chest radiograph, pulmonary oedema (that cannot be explained by fluid overload or cardiac failure) and hypoxemic respiratory failure<sup>3</sup>. The mortality of ARDS appears to be approximately 40–50%, although this figure varies greatly between different studies. It is unclear whether there has been any overall improvement in mortality over time<sup>4,5</sup>. To date, only the use of extracorporeal membrane oxygenation, prone positioning and low-tidal

volume ventilation have shown a reduction in mortality amongst ARDS patients, whereas several other innovative ventilatory approaches such as high-frequency oscillatory ventilation and recruitment manoeuvres yielded disappointing results<sup>6–11</sup>.

Neuromuscular blocking agents (NMBAs) are used in 25–40% of patients with ARDS and may improve both oxygenation and patient mortality<sup>12,13</sup>. They act at the neuromuscular junction and are categorized as either depolarizing or non-depolarizing agents depending on their mode of action. Depolarizing agents create a continuous depolarization by acting as agonists at the acetylcholine (ACh) receptors. Non-depolarizing agents prevent the transmission of neural impulses by acting as competitive antagonists at the ACh receptors. Both induce a muscular paralysis, but whilst depolarizing muscle relaxants are primarily used during intubation as a bolus, NMBAs are frequently administered as continuous infusions in order to help facilitate mechanical ventilation<sup>14,15</sup>.

Cisatracurium besylate, a non-depolarizing muscle relaxant, which became available at the end of the last millennium, is one of the ten stereoisomers of atracurium (1R cis, 1R'cis). It is a benzylisoquinolinium compound that functions as a non-depolarizing NMBA and has an intermediate duration of action relative to other neuromuscular blockers. Cisatracurium degrades at physiological pH via Hofmann elimination. Therefore, the elimination of cisatracurium may be from both plasma and tissues. It has been demonstrated that cisatracurium infusions provide satisfactory neuromuscular blockade in

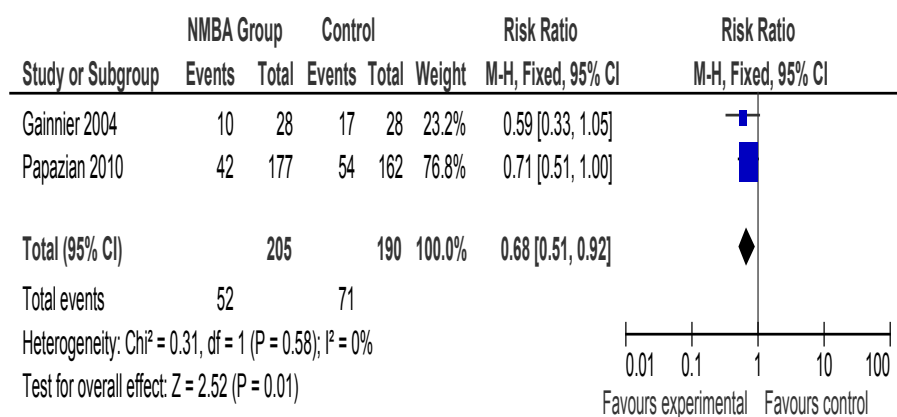
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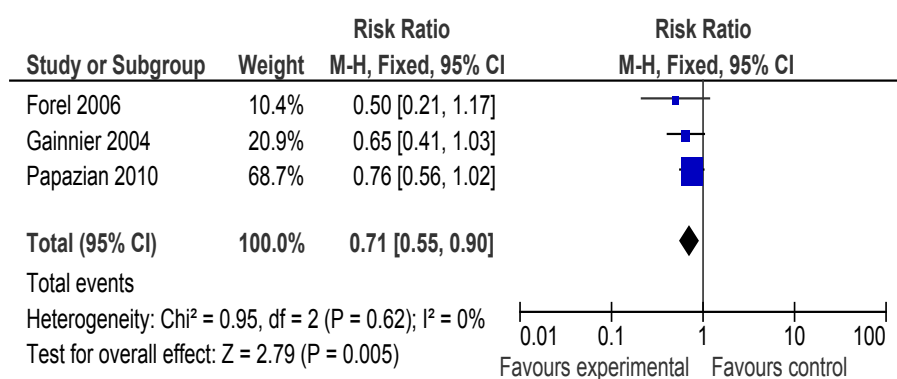
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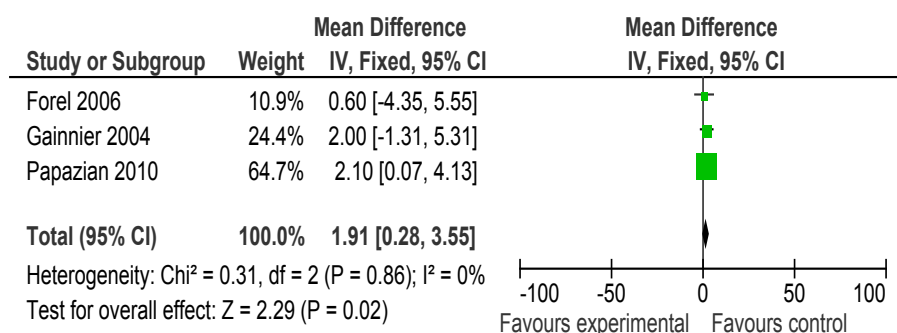




**Figure 1:** Risk of 28-day all-cause mortality.



**Figure 2:** Risk of ICU mortality.



**Figure 3:** Number of ventilator-free days at 28 days.

provided for mortality on a study-by-study basis irrespective of the length.

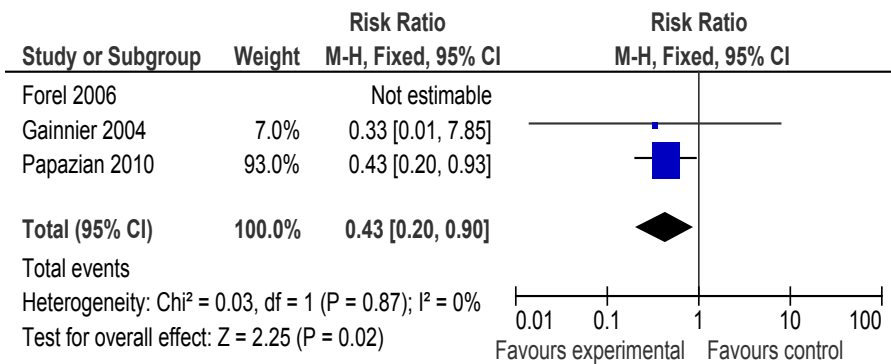
NMBAs did not show any significant effect on the duration of mechanical ventilation (RR 1.14, 95% CI = -4.07-6.35,  $I^2 = 0\%$ ) (Figure 6) or on the number of cases of new-onset critical illness neuromyopathy (RR 1.13, 95% CI = 0.76-1.67,  $I^2 = 0\%$ ) (Figure 7).

### Discussion

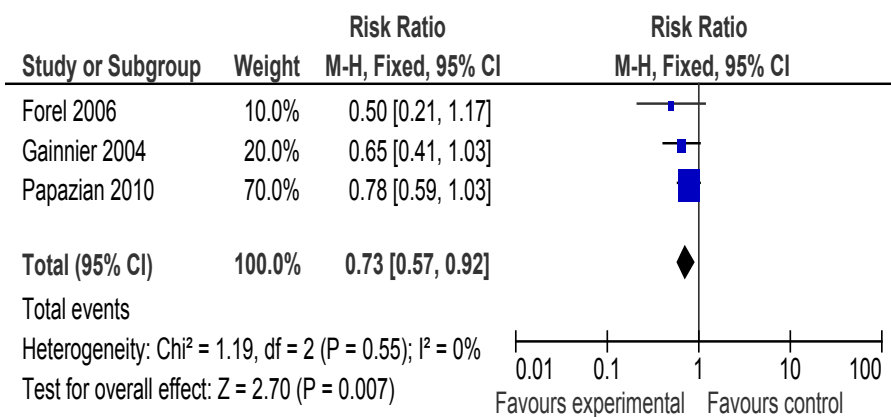
Overall, our results showed that the early use of cisatracurium infusion for a short period of time was able to produce a statistically significant reduction in mortality in patients with ARDS. Treatment with cisatracurium also increased the number of ventilator-free days and reduced the incidence of new-onset barotrauma.

The meta-analysis pooled data from three studies containing 431 patients. Whilst many of the results generated from this analysis were statistically significant, it is important to note that the total sample size was small. Furthermore, these trials were all produced by the same group, with both Forel<sup>19</sup> and Gainnier<sup>23</sup> being precursor studies to the larger Papazian<sup>21</sup> trial. Whilst all three were multicentre trials, the same centres took part in multiple studies and they were all carried out within a limited number of intensive care units in Southern France. As a consequence of this, the generalizability of the results is questionable, and further randomized trials need to be carried out to establish whether these results are reproducible outside of these centres and to increase the limited quantity of data currently available for analysis.

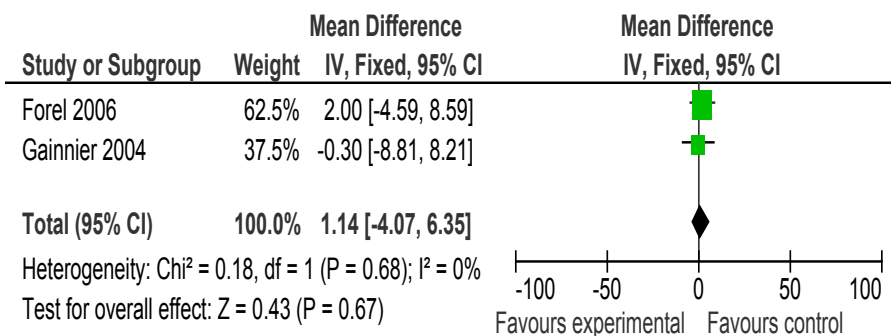
The Gainnier trial<sup>23</sup> was carried out in 2004 primarily to assess whether NMBAs improved gas exchange in ARDS patients. It was the first randomized controlled trial to investigate the effects of NMBAs in ARDS patients, but was open label and contained only 56 patients. However, the results were promising and showed an association between cisatracurium use and improved oxygenation. Subsequently, Forel and colleagues<sup>19</sup> carried out a second randomized controlled trial, this time investigating the effects cisatracurium had on pulmonary and systemic inflammatory responses. This trial was also small scale, but it was blinded and also used a placebo rather than just conventional therapy for the control group. The results were again encouraging and showed that cisatracurium usage decreased the inflammatory response in ARDS patients. These two early studies both collected a wide range of data beyond their primary outcome measures including for mortality and adverse events, and these data were included in our meta-analysis.



**Figure 4:** Risk of new-onset barotraumas.



**Figure 5:** Risk of overall mortality.



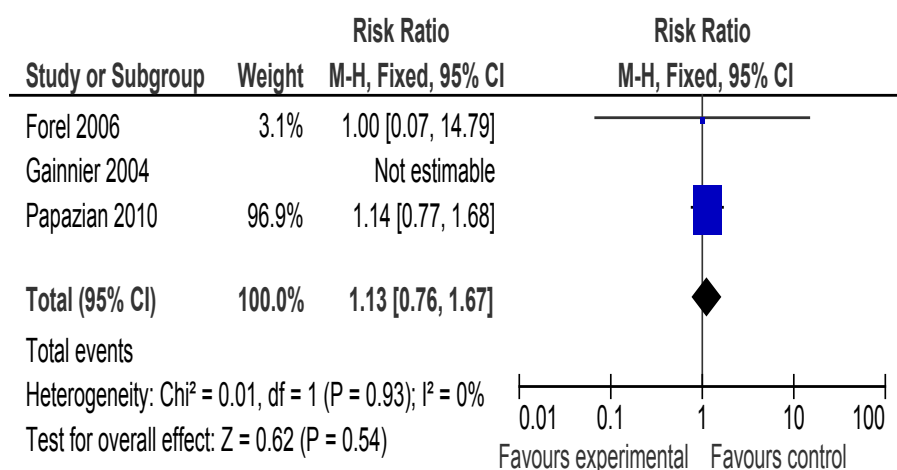
**Figure 6:** Duration of mechanical ventilation.

By far, the largest randomized controlled trial and the only one designed to specifically investigate mortality was that carried out by Papazian and colleagues<sup>21</sup>. This double-blinded trial was carried out across 20 units, far more than participated in the previous two trials. It was designed to be sufficiently powered to assess any association between the early and short

use of cisatracurium and mortality. However, due to the mortality in the placebo group being lower than in the previous studies, the study ended up underpowered. Our meta-analysis was able to pool the data from all three trials undertaken by this group and thus increase the power sufficiently to give us results that were statistically significant.

Although we can show a statistically significant improvement in outcome, it is not clear what is the exact mechanism behind this benefit. Improved oxygenation, reduced inflammatory response and reduced respiratory complications could be argued; however these were shown not to be significant determinants of outcome in large randomized controlled trials<sup>8,11</sup>. Indeed, the decreased rate of pulmonary complications in the NMBA groups in all three trials could be interpreted as protective effects of cisatracurium to prevent unintended consequences of VILI caused by inadequate ventilation strategy. Contrary to other major studies, the three trials used volume assist-control mode of ventilation, which is controversial in its ability to induce alveolar overdistension, aggravating ventilator-induced lung injury and barotrauma<sup>25</sup>.

Some advantages of the studies were that all had similar ventilation protocol and used 48-h infusions of cisatracurium. However, there was significant heterogeneity in the infusion rate and initial bolus dose of cisatracurium administered. It is also unclear whether the infusion rates were sufficient to induce deep neuromuscular blockade in all patients, as only two of the smaller studies employed neuromuscular blockade depth monitoring. It is also worth noting that as our meta-analysis focused on cisatracurium as the neuromuscular blocker in their intervention groups, the results only apply to this drug rather than necessarily to NMBAs as a whole. Other NMBAs such as atracurium, vecuronium, pancuronium and rocuronium are frequently used in clinical practice so it is important that the efficacy and safety of these alternative agents are also evaluated in future trials. A decade ago in the United States, vecuronium was used frequently or routinely versus pancuronium rocuronium<sup>26</sup>. There is no reliable data available about whether this has



**Figure 7:** Risk of new-onset critical illness neuromyopathy.

changed over the years, or whether this is the case in other parts of the developed world. When asked about decision-making, clinicians responded that they were more likely to choose an NMBA based on their clinical experience and preference than on patient-specific factors<sup>26</sup>. Therefore, we should exercise caution when generalizing the results.

Whilst carrying out our literature search, the only other relevant studies we encountered were two retrospective analyses: one from Arroliga and others and the other one from the French group led by Forel<sup>27,28</sup>. The Arroliga study initially suggested that NMBA use increased both the duration of mechanical ventilation and the 60-day mortality; however following adjustment for the baseline variables, no significant association was observed for either of these measures<sup>27</sup>. Nonetheless, the study did raise an important question: Are NMBAs more frequently used as a rescue therapy in ARDS once other options have been exhausted rather than as an early intervention? Arroliga's study found NMBA use to be correlated with variables that suggested a greater degree of acuity, such as a higher APACHE III score<sup>27</sup>. The results of their analysis suggested that NMBAs are more likely to be used in the most critically ill patients

in clinical practice<sup>27</sup>. The use of NMBAs as a rescue therapy contrasts with their usage in the three studies within this meta-analysis where they were given to patients early on and with an established protocol. This is an important consideration when determining the optimum use of NMBAs in the management of ALI/ARDS patients since our meta-analysis shows they could provide a significant mortality benefit. However, these results relate to the early use of a continuous infusion of NMBAs, as opposed to their use as an emergency therapy, which we suspect is how they are currently widely used. Forel et al. retrospectively analysed the data from the Papazian trial to investigate whether bacterial VAP has got any effect on mortality in ARDS and to determine what are the risk factors for VAP<sup>28</sup>. Importantly for us, they did not find any adverse effect of early short-term use of cisatracurium on VAP rates, which is in contrast with previous studies where NMBA use at any timepoint in non-selected ALI/ARDS patients was associated with increased rate of new infections<sup>28,29</sup>.

The primary concern with using neuromuscular blocking drugs is the possibility that they may cause critical illness neuromyopathies<sup>14,30</sup>. The presented data suggest that the use

of cisatracurium is safe in ARDS patients, with the analysis showing that it did not have a significant effect on the number of cases of neuromyopathy that occurred. However, the tool employed in the Papazian study to look for critical illness polyneuropathy has been questioned and so has been the timeframe of the screening. Indeed, only 293 patients were included in this outcome analysis (Figure 7), and a larger sample size would be desirable to increase the strength of this conclusion given the seriousness of the concerns.

### Conclusion

This meta-analysis showed that the early, short use of a continuous infusion of cisatracurium led to a statistically significant reduction in mortality in ARDS patients. These results demonstrate that this can be a valuable intervention in the treatment of ARDS. Further trials assessing the use of NMBAs are recommended to test the reproducibility of the studies included and to further assess the concerns over the safety of this intervention.

### Abbreviations list

ACh, acetylcholine; AECC, American-European Consensus Conference; ARDS, acute respiratory distress syndrome; CENTRAL, Cochrane Central Register of Controlled Trials; NMBA, neuromuscular blocking agent

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