Systematic review and network meta-analysis of neuromuscular blocking agents to facilitate endotracheal intubation in children.

Verheyden C ¹, Geniets B ², Driessen JJ ³, Vanlinthout L ^{3,4}, Berghmans J ¹, Hens N.⁴.

¹ University of Leuven, Dept of Anaesthesiology, Leuven, Belgium, ² GZA Hospitals, Antwerp, ³ University Medical Center Nijmegen, Dept of Anaesthesiology, Nijmegen, Netherlands, ⁴ University of Hasselt, Interuniversity Institute for Biostatistics and statistical Bioinformatics, Leuven-Hasselt, Belgium,

Successful intubation without using neuromuscular blocking agents has been established during anaesthesia induction for elective procedures on healthy children with normal airway anatomy. However, the outcomes from average unproblematic patients cannot be extrapolated to emergency cases and those with airway abnormalities. Moreover, the doses and combinations of drugs used in many of the relaxant free intubation trials may put patients at risk to haemodynamic depression, especially when given to ill and debilitated children.

The benefit of using neuromuscular blocking agents to facilitate tracheal intubation in children remains unclear, owing to variations in design and outcomes between trials. By combining the available evidence and investigating reasons for between-study heterogeneity, we aimed to establish whether scientific findings are consistent and can be generalized across populations, settings and treatment variations.

Some systematic reviews compare only two interventions, in which conventional pair-wise meta-analysis may be conducted. Since recently, effectiveness of many or all available interventions for a given condition can be compared, using network meta-analysis.

METHODS

A systematic review was performed according to the guidelines outlined in the PRISMA statements [1]. For our analysis, we included only RCTs that compared intubation conditions created by Rocuronium (Rc), Suxamethonium (Sx), Mivacurium (Mv), Atracurium (Atr), Vecuronium (Vec), and Cis-atracurium (c-Atr) in children 1-12 y. Excellent intubation conditions were used as the clinical endpoint/outcome.

We explored heterogeneity using both pair-wise meta-analysis on subgroups and meta-regression analysis on relaxant groups. Trial sequential analysis allowed to calculate the power and indicate the need for additional studies.

We modelled the outcomes from the treatment groups of the RCTs included, using a random-effects model and established the relations among the odds ratios (ORs) across studies making different comparisons. This method combines direct and indirect evidence for any given pair of treatments (Figure 1). Potential characteristics associated with variation in study outcomes were explored, such as age, time to intubation, anaesthetic technique used for induction and continent of study. Meta-analysis was done using both, frequentist (Stata 15.0) and Bayesian (Winbugs 1.4.3) approaches. We used p values less than 0.05 and 95% CIs.

Figure 1. If we assume that AB trials and the AC trials are comparable on effect modifiers, an unbiased indirect estimate for the relative effect of C versus B can be obtained from the estimates of the effect of B versus A and the effect of C versus A.

RESULTS and CONCLUSION(S)

We included 63 eligible trials of 4934 participants. The use of neuromuscular blockers increased the likelihood of excellent intubation conditions ($p<0.001$). Intubation conditions depended upon the choice and dose of the relaxant, timing of its administration, the use of propofol and/or inhalational agents, and patients' age. Although opioids can have a major influence on the quality of intubation, no such association could be demonstrated when using rocuronium or suxamethonium to facilitate tracheal intubation. Lack of outcome assessor's blinding of the proved to interfere with assessment of treatment effect. Network meta-analysis allowed to interpret the wider picture of evidence and to estimate the relative merits of different interventions.

Figure 2. Network of eligible comparisons of the multiple-treatment meta-analysis regarding efficacy of NMBA to create excellent intubation conditions. The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants.

Figure 3. Forest plot displaying odds ratios (●) and their 95% credibility intervals (solid lines) for the intubation conditions created by different interventions versus a common reference treatment, i.e. suxamethonium 1.0 mg·kg⁻¹ (represented on the plot as a vertical red line).

[1] Hutton et al. Ann Intern Med. 2015; 162: 777-84