# Supplementary Online Content

Guihard B, Chollet-Xémard C, Lakhnati P. Effect of rocuronium vs succinylcholine on endotracheal intubation success rate among patients undergoing out-of-hospital rapid sequence intubation: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2019.18254

Statistical analysis plan

This supplementary material has been provided by the authors to give readers additional information about their work.

# Statistical Analysis Plan

# Comparison of Succinylcholine and Rocuronium for Prehospital Emergency Intubation

# (The CURASMUR study)

# A no inferiority Randomized Clinical Trial

| VERSION | DATE | REASON FOR UPDATE |
|---|---|---|
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# TABLE DES MATIERES

## Study design

This is a randomized non-inferiority trial comparing two muscle relaxants (Rocuronium versus Succinylcholine)used for intubation in pre-hospital setting . The study is a single blind study (patient blinded) (patient).

Randomization was defined by block and stratified by center. Numbered, opaque and sealed envelopes were used in each ambulance for the assignment of the type of curares.

## Objectives

### Main objective

The main objective of the study is to demonstrate that emergency intubation conditions are non-inferior when Rocuronium is used in comparison with Succinylcholine in fast sequence induction sedation.

### Secondary objectives

Secondary objectives assessing effectiveness of Rocuronium are:

- Assessment of the quality of direct laryngoscopy, using the classification of Cormack and Lehane
- Measure of the overall difficulty of the intubation process evaluated by the difficult intubation score (IDS)
- Assessment of intubation conditions using the Copenhagen score
- Assessment of the need for use of difficult intubation devices (Stylet, Gum Elastic bougie, Intubating laryngeal mask airway, Cricothyrotomy)
- Assesemnt of the tolerance of the 2 treatments, comparing the rate of complications observed with the use of Rocuronium or Succinylcholine

## Outcomes

### Primary outcome

The primary outcome is the proportion of successful intubation at first laryngoscopy in the two groups.

### Secondary outcomes

- Distribution of grades of Cormack and Lehane classification in 2 treatment arms
- The difficult intubation score (IDS) in the 2 treatment groups
- Copenhagen score in the 2 treatment groups
- Proportion of use of difficult intubation devices (Stylet, Gum Elastic bougie, Intubating laryngeal mask airway, Cricothyrotomy) in the 2 treatment groups
- Proportion of immediate complications (in the first 15 minutes) following intubation according to the type of paralytic agent used: hypotension, cardiac arrhythmias, cardiac arrest, pulmonary inhalation, occurrence of episodes of arterial hypoxemia, allergic reaction

## Eligibility criteria

### Inclusion criteria

All adult patients with spontaneous cardiac activity requiring endotracheal intubation in the pre hospital setting were included in the study.

### Non-inclusion criteria

- Minor patients- Pregnant women
- Presence of a contraindication to succinylcholine:
    - Personal or family history of recognized malignant hyperthermia
    - Allergy recognized with succinylcholine
    - Congenital muscle damage
    - Myasthenia
    - Certain hyperkalemia
    - Open-eye ophthalmic surgery
    - Congenital deficiency in known plasma pseudocholinesterases
- Presence of a contraindication to Rocuronium: recognized allergy to Rocuronium
- Presence of a contraindication to Sugammadex: allergy recognized to Sugammadex
- Patient not affiliated to a social insurance (beneficiary or beneficiary)

## Sample size

The assessment of the number of patients required was made assuming a proportion of intubation successful at the first laryngoscopy of 75% and a margin of non-inferiority of 7%.

Under these assumptions, the number of subjects to be included was 602 patients per group (1204 patients in total) to demonstrate that the intubation rate at the first trial is not inferior in the Rocuronium group compared with the Succinylcholine group at unilateral alpha risk of 2.5% and a beta risk of 20%.

An additional inclusion safety margin related to the risk of protocol deviations related to "field" inclusion and emergency randomization increased the number of subjects to be included to 650 per group (1300 to total).

## Descriptive analyses

Characteristics of patients in each group will be summarized in a descriptive table. Descriptive statistical analysis will include for each quantitative variable: the mean, the standard deviation, the minimums and maximums, as well as the median and the quartiles. The qualitative variables will be expressed as frequencies and proportions. The standardized difference between the two groups will also be calculated for each variable and presented in this same table.

A descriptive analysis by center will be carried out. Patient characteristics included by center will be presented in a descriptive table.

## Management of missing data

Prior to the analyses, a completion of the missing data will be carried out, if necessary, using a multiple imputation method. The hypothesis adopted regarding the mechanism of occurrence of the missing data will be a so-called Missing At Random (MAR) hypothesis. The Missing Not At Random hypothesis (MNAR) will also be tested. Imputations will be made for the primary outcome, the secondary outcomes, and the covariates.

## Statistical analyses

Analyses of the primary outcome and the secondary outcomes will be presented in a summary table. Qualitative variables will be presented as frequencies and proportions. Quantitative variables will be presented as mean and standard deviation. The ordinal variables will be presented as median and quartiles.

All statistical analyses will be performed using SAS 9.4 software (SAS Institute Cary Inc).

### Analysis of primary outcome

The non-inferiority between the proportions of successful intubation in the two treatment arms will be tested using the Dunnett and Gent method. The equivalence test will be a one-sided test based on the assumption of a non-inferiority margin δ of 7%. The one-sided confidence interval at 97.5% of the difference in percentages of successful intubation will also be calculated using Wald's method. This method allows control of Type I error in a non-inferiority setting. The analysis will be performed per protocol, as recommended for non-inferiority trials, and supplemented with an intention-to-treat analysis.

### Analyses of secondary outcomes

#### Comparisons of the Cormack and Lehane Classification in Treatment Arms

The classification of Cormack and Lehane evaluates the quality of the direct laryngoscopy and is coded in 4 modalities: grade 1 to 4. It is an ordinal variable with 4 modalities. The comparison of this classification between the two treatment arms will be performed using a Mann-Whitney test, adapted for ordinal variables.

#### Comparison of Intubation Difficult Score (IDS) in both treatment arms

The Intubation Difficult score (IDS) measures the overall difficulty of the intubation process. This score is a discrete quantitative variable. The comparison of this score in the two treatment arms will

be performed using a Student's t-test after checking the normality of the distributions and the equality of the variances.

### Comparison of Copenhagen scores in the two treatment arms

The Copenhagen score characterizes the conditions of intubation and is coded in 3 modalities. This is an ordinal variable with 3 modalities. The comparison of the Copenhagen score between the two treatment arms will be performed using a Mann-Whitney test, adapted for ordinal variables.

### Comparisons of Intubation Devices use rates in the treatment arms

Difficult intubation devices include:

- The use of Stylet
- The use of Gum Elastic bougie
- The use of Intubating laryngeal mask airway
- Cricothyrotomy

These are dummy variables with 2 modalities. The comparison of proportions for each device will be performed using a Chi2 test or Fisher's exact test depending on the application conditions.

### Comparisons of proportions of immediate complications in treatment arms

Immediate complications include the occurrence:

- Low blood pressure
- Severe Cardiac arrhythmia
- Cardiac arrest
- Pulmonary aspiration
- Episodes of arterial hypoxemia
- Allergic reaction.

These are dummy variables with 2 modalities. The comparison of proportions for each complication will be performed using a Chi2 test or an exact Fisher test according to the conditions of application.

## Adverse events

The proportions of adverse events (serious and non-severe), their intensity, study imputation, and outcome will be described in a summary table, and compared between the two treatment arms, using a Chi2 or Fisher's exact test depending on the conditions of application.

## Concomitant treatments

The frequency and proportion of treatments received in each treatment arm will be described in a descriptive table. The comparison of each proportion between the two treatment arms will be performed using a Chi2 test or an exact Fisher test according to the conditions of application.

In the Rocuronium group, the frequency and proportion of patients receiving Sugammadex will be estimated as well as the 95% confidence interval of this proportion.

## Subgroup analyses

No subgroup analysis will be performed.

## Sensitivity analysis

A sensitivity analysis of the primary outcome will be made by intent to treat using the method described in the primary endpoint analysis.

## Tables templates

The table templates are shown below.

**Table 1: Characteristics of patients at baseline in the CURASMUR study**

| | **Rocuronium (N=)** | **Succinylcholine (N=)** | **Std diff.** |
|---|---|---|---|
| Age, mean(SD) | | | |
| Sex, n(%) | | | |
| … | | | |
| … | | | |

**Table 2: Characteristics of patients at baseline in the CURASMUR study by center**

| | **Centre 1 (N=)** | **…** | **Centre k (N =)** |
|---|---|---|---|
| Age, mean(SD) | | | |
| Sex, n(%) | | | |
| … | | | |
| …. | | | |

198 **Table 3: Comparison of the characteristics and complication of intubation according to the treatment arm**

| | Rocuronium (N=) | Succinylcholine (N=) | p-value |
|---|---|---|---|
| Successful intubation, n(%) | | | |
| | | | |
| Cormack and Lehane, median (IQR) | | | |
| IDS, mean (SD) | | | |
| Copenhaguen Score, median (IQR) | | | |
| | | | |
| Use of Stylet, n(%) | | | |
| Use of Gum Elastic bougie, n(%) | | | |
| Use of Intubating laryngeal mask airway | | | |
| Cricothyrotomy, n(%) | | | |
| | | | |
| Low blood pressure, n(%) | | | |
| Cardiac arrest, n(%) | | | |
| Pulmonary inhalation, n(%) | | | |
| Episodes of arterial hypoxemia, n(%) | | | |
| Allergic reaction, n(%) | | | |

199

200 **Table 4: Comparison of adverse events (AEs) according to the treatment arm**

| | Rocuronium (N=) | Succinylcholine (N=) | p-value |
|---|---|---|---|
| Adverse events, n(%) | | | |
| Severe Adverse Events, n(%) | | | |
| | | | |
| Intensity of Adverse Events | | | |
| Slight | | | |
| Moderate | | | |
| | | | |
| Imputable to the study | | | |
| Possible | | | |
| Doubtful | | | |
| Excluded | | | |
| Not assessable | | | |
| | | | |
| Evolution | | | |
| Healing without sequelae | | | |
| Healing with sequelae | | | |
| Not healed yet | | | |
| Aggravation | | | |
| Death | | | |
| Unknown | | | |

201

202 **Table 5: Detail of adverse events according to the treatment arm**

| | Rocuronium (N=) | Succinylcholine (N=) |
|---|---|---|
| Shock | | |
| Hypotension | | |
| Hypoxemia | | |
| … | | |

203

204

205 **Table 6: Comparison of concomitant treatments according to the treatment arm**

| | Rocuronium (N=) | Succinylcholine (N=) | p-value |
|---|---|---|---|
| Dobutamin, n(%) | | | |
| Ephedrin, n(%) | | | |
| Morphin, n(%) | | | |
| … | | | |

206