Statistical Analysis Plan

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Title: ***Time to Adapt in the Pandemic Era: A Prospective Randomized Study Comparing Time to Intubate With and Without the Barrier Box***

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National Clinical Trial Number: NCT04411056

Sample size calculation
Sample size calculation was done by using the two means equation in the Power and Sample Size Calculation program (Dupont and Plummer, 1990). Based on a study by Teoh et. al., (2019), the mean of intubation time for Glidescope was 31.2 seconds and Airway Scope was 20.6 seconds. A clinically significant effect of 10 seconds would be of interest. The two-tailed hypothesis testing concluded that each group needed 36 subjects to achieve a power of 80%, with an error rate of 5%. A total of 90 subjects will be enrolled in this study with an estimated dropout rate set at 20%, 45 subjects will be enrolled in each group.

Suggested citation for Power and Sample Size:
Dupont WD, Plummer WD: 'Power and Sample Size Calculations: A Review and Computer Program', Controlled Clinical Trials 1990; 11:116-28.
Reference article;
Teoh WHL, Saxena S, Shah MK, Sia ATH. Comparison of three videolaryngoscopes: pentax Airway Scope, C-MAC, Glidescope vs the Macintosh laryngoscope for tracheal intubation, Anesthesia. 2010; 65: 1126-1132.

It is a standard practice to include a dropout rate of 20% for clinical trials so that the power of the study will not be affected by dropouts, missing data and other study deviations (https://online.stat.psu.edu/stat509/node/47/).

May 5, 2020 Statistical Consultant KV

The study plans to enroll approximately 72 subjects to two groups with 36 subjects in each group. This sample size is based on the estimated time difference of 10 seconds between intubation times with and without the box. (Protocol April 30, 2020)

Randomization:

Subjects will be randomized by block randomization. Randomization will be done by a random number generated computer program by someone not involved in the research. The randomization schedule will be placed in sealed envelopes to be concealed from the researcher until time of verbal consent.

Sealed Envelope Ltd. 2019. Simple randomisation service. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/ [Accessed 6 May 2020].

Statistical Software

R 3.5.3 software will be used for statistical analysis.

Non-Inferiority Study Design

Hypothesis

Use of the barrier box prolongs the mean TTI by more than 15 s compared to a control group with no barrier box

HO: Mean TTI changes with barrier box

HA: Mean TTI does not change with barrier box

Non-inferiority margin: Our research team decided to use 15 s as non-inferiority margin. The premise of our non-inferiority study is to compare the mean TTI and infer if the additional time taken for airway manipulation with a barrier box is within acceptable non-inferiority margin between the means of both the groups (Box vs No Box). Non-inferiority margin of 15 s is considered acceptable while comparing airway manipulation in both the groups based on our clinical experience and pilot study data. Our literature review showed that this non-inferiority margin ($\Delta = 15$ s) would be within safe period of apnea tolerated by most patients (Moon et.al.)

Moon TS, Tai K, Kim A, Gonzales MX, Lu R, Pak T, et al. Apneic Oxygenation During Prolonged Laryngoscopy in Obese Patients: a Randomized, Double-Blinded, Controlled Trial of Nasal Cannula Oxygen Administration. Obes Surg. 2019;29(12):3992–9 Available from: https://pubmed.ncbi.nlm.nih.gov/31317460. [cited 2020 Jun 29].

Baseline data

Descriptive statistics for baseline demographics will include:

- Age in years- mean (standard deviation)
- BMI - mean (standard deviation)
- Sex (male or female) – frequency, number of participants
- American Society of Anesthesiology (ASA) Physical Status – frequency, number of participants. ASA Physical Status is a classification system to assess a patient's pre-anesthesia medical co-morbidities, and helps predict perioperative risk when used with other risk factors such as frailty, level of deconditioning and type of surgery.
    - ASA 1 – a normal healthy patient
    - ASA 2 – a patient with mild systemic disease
    - ASA 3 – A patient with severe systemic disease
    - The study will exclude patients who are ASA 4 (a patient with severe systemic disease that is a constant threat to life) or ASA 5 (a moribund patient who is not expected to survive without the operation).

Continuous variables of age and body mass index (BMI) will be reported as mean and standard deviation. Categorical variables of Gender (Sex) and ASA Physical Status will be reported in frequency tables.

For continuous variables, the two groups ("barrier box" or "no barrier box") will be compared using unpaired two-sample t-tests, if data meets assumptions for normally distributed data within each group and homogeneity of variances (equal variance between groups)

For categorical variables, the two groups (“barrier box” or “no barrier box”) at baseline will be compared using chi-square test of independence.

Primary endpoint

The primary end point is time to intubate (TTI) in seconds, from loss of twitch to confirmation of end tidal carbon dioxide.

TTI will be collected by an independent provider (registered nurse) not directly involved in airway management. The TTI is used as an outcome measure as it is an objective variable that can be measured and helps us in assessment of airway manipulation with a barrier box. We plan to use objective end points to eliminate inter- observer variability.

For the primary endpoint, mean TTI and 95% confidence intervals will be assessed and compared in the two groups, “barrier box” and control with “no barrier box”.

An unpaired two-sample single-sided t-test will be used to test our non- inferiority hypothesis. The TTI of the barrier box group is expected to be higher than the mean TTI of control the group. Analysis will include two independent sample comparison of means using one sided t-test in R.

The t-test will be done based on assumptions that the sample has no dependence between subjects in the control group and the barrier box group. Similar variance in both the groups will be confirmed by Levine’s test. With the sample size > 30, samples are expected to be from a population with a normal distribution. Results will be considered statistically significant when $p < 0.05$.

If the difference of the mean TTI between the groups is less than the non-inferiority margin of 15seconds, then the null hypothesis will be rejected.

Secondary endpoints and statistical analysis include:

- Attempts at intubation
    - assessed as frequency (percentage) of patients intubated on first attempt.
- Need for bag mask ventilation (yes or no) during induction, defined as the time taken from propofol bolus to loss of twitches measured with a peripheral nerve stimulator.
    - assessed as frequency (number) of patients.
- Lowest oxygen saturation during induction (Lowest peripheral capillary oxygen saturation during induction, defined as the time taken from propofol bolus to loss of twitches measured with a peripheral nerve stimulator.
    - assessed as mean and standard deviation
- Induction time - defined as the time taken from propofol bolus to loss of twitches measured with a peripheral nerve stimulator.
    - assessed as mean (in seconds) and 95% confidence intervals

For continuous variables, the two groups ("barrier box" or "no barrier box") will be compared using unpaired two-sample t-tests, if data meets assumptions for normally distributed data within each group and homogeneity of variances (equal variance between groups)

For categorical variable, the two groups ("barrier box" or "no barrier box") will be compared using chi-square test of independence.

Airway assessment data will be collected for the two groups ("barrier box" or "no barrier box") as frequency data (number of patients) and will include:

- Mallampati score (scale of 0 to 4) used to assess and prepare for possible difficult intubation of participants who score high. Lower scores are less likely to have a difficult intubation, and higher scores are more likely to have a difficult intubation.
- Number of patients will be assessed in both groups for each of these classes:
    - Mallampati 0 (Any part of the epiglottis is visible)
    - Mallampati 1 (soft palate, uvula, and pillars are visible)
    - Mallampati 2 (soft palate and uvula are visible)
    - Mallampati 3 (only the soft palate and base of the uvula are visible)
    - Mallampati 4 (only the hard palate is visible)

- Thyromental Distance (TMD) > 3 finger breadth
    - TMD is the distance from the thyroid notch to the chin when the head is extended. TMD is used to assess and prepare for possible difficult intubation of participants who are less than or equal to 3 finger breadth. A distance of greater than 3 finger breadth may be less likely to have a difficult airway or airway constriction

  Number of patients with TMD > 3 finger breadth will be assessed in both groups

- Inter incisor distance > 3 finger breadth
    - Inter incisor distance is the distance between the upper and lower teeth of the open mouth of a patient. Inter incisor distance is used to assess and prepare for possible difficult intubation of participants who are less than or equal to 3 finger breadth. A distance greater than 3 finger breadth may be less likely to have a difficult airway or airway constriction

  Number of patients with Inter incisor distance > 3 finger breadth will be assessed in both groups.

- Neck range of motion (Full or Restricted)
    - Neck range of motion is the degree of movement in the neck - how much the head can flex (bend forward), extend (tilt backwards), and rotate side to side. Full range of motion is less likely for a difficult airway or airway constriction than Restricted range of motion.

  Number of patients with Neck range of motion (categorized as full or restricted) will be assessed in both groups.

For these airway assessment categorical variables, the two groups ("barrier box" or "no barrier box") will be compared using chi-square test of independence.