McGRATH MAC videolaryngoscope versus Macintosh laryngoscope for orotracheal intubation in intensive care patients: the randomised multicentre MACMAN trial study protocol

Arthur Bailly,¹ Jean Baptiste Lascarrou,¹ Aurelie Le Thuaut,²,³ Julie Boisrame-Helms,⁴,⁵ Toufik Kamel,⁶ Emmanuelle Mercier,⁷ Jean Damien Ricard,⁸,⁹ Virginie Lemiale,¹⁰ Benoit Champigneulle,¹¹ Jean Reignier,¹² for the Clinical Research in Intensive Care and Sepsis (CRICS) Group

ABSTRACT

Introduction: Critically ill patients with acute respiratory, neurological or cardiovascular failure requiring invasive mechanical ventilation are at high risk of difficult intubation and have organ dysfunctions associated with complications of intubation and anaesthesia such as hypotension and hypoxaemia. The complication rate increases with the number of intubation attempts. Videolaryngoscopy improves elective orotracheal intubation. McGRATH MAC is the lightest videolaryngoscope and the most similar to the Macintosh laryngoscope. The primary goal of this trial was to determine whether videolaryngoscopy increased the frequency of successful first-pass intubation in critically ill patients, compared to direct view Macintosh laryngoscopy.

Methods and analysis: MACMAN is a multicentre, open-label, randomised controlled superiority trial. Consecutive patients requiring intubation are randomly allocated to either the McGRATH MAC videolaryngoscope or the Macintosh laryngoscope, with stratification by centre and operator experience. The expected frequency of successful first-pass intubation is 65% in the Macintosh group and 80% in the videolaryngoscope group. With α set at 5%, to achieve 90% power for detecting this difference, 185 patients are needed in each group (370 in all). The primary outcome is the proportion of patients with a primary outcome. Use of successful first-pass intubation as the primary outcome. Powered to detect a 15% increase in the first-pass intubation success rate with videolaryngoscopy; therefore, a smaller but possibly clinically important true difference might be missed.

Thus, patient safety should benefit. Further studies would be warranted to determine whether videolaryngoscopy is also beneficial in the emergency room and for prehospital emergency care.

Trial registration number: NCT02413723; Pre-results.

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.¹

(A) Endotracheal intubation (ETI) is performed in intensive care units (ICUs) as an emergency procedure in patients with unstable critical illnesses. This setting is associated with an increased frequency of difficult intubation, compared to intubation for surgery (10% to 20% vs 3% to 5%).²–⁴ The combined presence in many ICU patients of multiple organ dysfunctions, a small physiological reserve and a high risk of difficult intubation translates into a high frequency of intubation-related complications, ranging from 25% to 40%.²–⁵ The risk of complications increases with the number of intubation attempts.⁷–⁸
Several preventive measures are available for minimising the frequency and severity of intubation-related complications. Anaesthetic agents proven effective and safe for rapid sequence intubation (RSI)⁹–¹¹ must be used if not contraindicated. RSI requires the concomitant administration of a fast-acting neuromuscular blocker, that is, succinylcholine or rocuronium, to facilitate the procedure and limit the risk of gastric content aspiration.¹² Also recommended is preoxygenation for 3 min at least, if needed using non-invasive ventilation (NIV).¹³ Finally, fluid resuscitation and vasopressor support must be started early to ensure haemodynamic stability during ETI. When used in combination as part of a standardised protocol, these measures considerably decrease the risk of complications.¹⁴ Many professional societies recommend the use of such a protocol, with training of all staff members and routine capnography before ETI.¹⁵ ¹⁶

The preventive measures described above decrease the risk of complications but fail to increase the frequency of successful first-pass ETI, a major determinant of intubation-related complications. Measures capable of increasing the frequency of successful first-pass ETI are needed. At present, use of a Macintosh laryngoscope with a metal blade is the reference standard for RSI.¹⁷ Over the past few years, however, videolaryngoscopes providing a full indirect view of the glottis have shown promise for facilitating ETI. Several studies compared various commercially available videolaryngoscopes, but most focused on ETI in the operating room for elective surgery. Their results suggest that benefits from videolaryngoscopy may be greatest in those patients at risk of difficult intubation.¹⁸–²¹ A 2014 meta-analysis suggested that videolaryngoscopy might be useful in the ICU.²² However, most of the studies had methodological weaknesses such as an observational²³–²⁵ or before/after²⁶ ²⁷ design or a randomised design but a small sample size and/or single-centre patient recruitment.²⁸ ²⁹ Studies performed more recently suggested benefits from videolaryngoscopy but either failed to routinely use neuromuscular blockade,³⁰ in contradiction of current guidelines, or included patients with highly specific characteristics.³¹ Furthermore, most studies of videolaryngoscopy were performed in the specific setting of difficult intubation (table 1).

(B) We chose the McGRATH MAC videolaryngoscope as the comparator, because its curved blade resembles that of the Macintosh laryngoscope and provides a direct view of the glottis and an indirect view via the camera, a combination that is helpful in the event of oropharyngeal malalignment. More specifically, our choice of the McGRATH MAC videolaryngoscope was based on three considerations:

- Intubators with experience using the Macintosh laryngoscope should be able to use the McGRATH MAC videolaryngoscope easily, as the blade curves are similar;
- The video monitor of the McGRATH MAC videolaryngoscope allows continuous supervision by a senior

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<th>Table 1: Recapitulation of previous studies on ETI with videolaryngoscopy in the intensive care unit or emergency department</th>
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CCM, critical care medicine; DL, direct laryngoscopy; ETI, endotracheal intubation; PCCM, pulmonary critical care medicine; PGY, post-graduate year physicians; VL, videolaryngoscopy.
intubator when ETI is performed by a junior intuba-
tor; and

- The McGRATH MAC videolaryngoscope is the light-
est weight videolaryngoscope available and can be
stored in a small prehospital-care ambulance.

The main purpose of this study is to evaluate whether
using videolaryngoscopy for ETI decreases the frequen-
cies of ETI failure and complications, by increasing the
first-pass ETI success rate via better visualisation of
the glottis, for all ETI procedures performed in ICU
patients.

Objectives

Primary objective. To determine whether McGRATH MAC
videolaryngoscopy improves the frequency of successful
first-pass ETI compared to Macintosh laryngoscopy in
patients admitted to the ICU and requiring orotracheal
intubation.

Secondary objectives: To determine whether McGRATH
MAC videolaryngoscopy for ETI decreases mortality and
morbidity and to assess the safety of McGRATH MAC
videolaryngoscopy.

Trial design

MACMAN is a multicentre, open-label, randomised con-
trolled superiority trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND
OUTCOMES

Study setting

The MACMAN trial is taking place in seven ICUs in
seven hospitals (five university and two general hospi-
tals) in France.

Eligibility criteria

Inclusion criteria

Patients must be admitted to an ICU and require mecha-
nical ventilation through an endotracheal tube.

Exclusion criteria

Patients are excluded if they meet one or more of the
following criteria:

- Contraindication to orotracheal intubation (eg, unsta-
tble spinal lesion);
- Insufficient time to include and randomise the
  patient (eg, because of cardiac arrest);
- Age <18 years;
- Pregnant or breastfeeding woman;
- Correctional facility inmate;
- Patient under guardianship;
- Patient without health insurance;
- Refusal of the patient or next of kin to participate in
  the study;
- Previous enrolment in a clinical randomised trial with
  intubation as the primary end point (including previ-
  ous inclusion in the present trial).

Interventions

Concomitant treatments in both groups

Patients are evaluated for factors known to predict diffi-
cult intubation and/or difficult ventilation (body mass
index, mouth opening, thyromental distance, Mallampati
score, history of snoring, missing teeth, sleep
apnoea syndrome). The results of this evaluation are
recorded in the electronic case report form (eCRF).

ETI is performed in both groups according to the
protocol outlined below (figure 1).

(A) Preoxygenation is achieved using the device
chosen by the doctor in charge of the patient:

- Bag valve mask delivering oxygen at a minimum flow
  of 15 L/min for at least 3 min.
- Non-rebreathing (high concentration) mask delivering
  oxygen at a minimum flow of 15 L/min for at least
  3 min.
- Ventilator in NIV mode providing 100% FiO2 for at
  least 3 min;
- High-flow nasal oxygen device (eg, Optiflow) delivering
  oxygen at a minimum flow of 60 L/min, with
  100% FiO2, for at least 3 min.

(B) Anaesthesia is then induced by injecting a hypno-
tic agent and a neuromuscular blocking agent. The
type and dosage of these drugs are at the discretion of
the intubating physician. Nevertheless, in agreement
with international38 and French guidelines,39 the follow-
ing two principles are applied:

- The preferred neuromuscular blocking agent in the
  absence of contraindications (eg, hyperkalaemia,
  burn injury more than 24 h earlier, spinal lesion or
  allergy) is succinylcholine in a dosage of 1 mg/kg.
The alternative is rocuronium 1 mg/kg, provided the
antidote sugammadex (16 mg/kg) is available.
- If possible, the hypnotic agent is either hypnomidate
  0.2–0.3 mg/kg or ketamine 1–2 mg/kg.

(C) Laryngoscopy is performed using the device allo-
cated at random:

- McGRATH MAC videolaryngoscope or
- Macintosh laryngoscope.

The first attempt with the McGRATH MAC videolaryn-
goscope is performed using the monitor. The final visu-
alisation method (direct or indirect via the monitor) is
recorded in the eCRF. The size of the endotracheal tube
and the size of the Macintosh laryngoscope are chosen
by the intubating physician.

(D) ETI is then performed. The cuff of the endo-
tracheal tube is inflated and the tube is connected to the
ventilator. If this first ETI attempt fails, the physician
chooses between repeating the same laryngoscopy
technique or switching to an alternative ETI technique.
The choice of the alternative ETI technique is at the
physician’s discretion and in accordance with French
guidelines.40 Each introduction of the laryngoscope into
the oral cavity of the patient is considered a separate
laryngoscopy attempt. Use of Sellick’s manoeuvre (press-
ure applied to the cricoid cartilage) during ETI is at the
discretion of the intubating physician and is recorded in
the eCRF. The intratracheal tube position is confirmed by analysing the capnography curve over four or more breathing cycles. Total ETI duration is defined as the time from anaesthesia induction initiation to observation of the first inflection on the expired capnography curve (confirming the intratracheal tube position). All items in the eCRF are analysed in real time by a person not involved in patient care. Offline analysis of laryngoscopic intubation is not performed.

All investigators attended a meeting about the trial before inclusion of the first patient. The investigators and coinvestigators received hands-on training in the use of the McGrath MAC videolaryngoscope and Macintosh laryngoscope.

Outcomes

**Primary outcome measure**
The primary outcome measure is the proportion of successful first-pass ETIs.

**Secondary outcome measures**
- Proportion of successful ETIs at any laryngoscopy attempt;
- Total time to successful ETI, defined as the time from anaesthesia induction initiation to confirmation of intratracheal endotracheal tube position based on the partial pressure of end-tidal exhaled carbon dioxide (PetCO₂);
- Cormack-Lehane grade of glottis visibility;
- Percentage of glottic opening scale score;
- Proportion of patients with difficult intubation;
- Proportion of patients intubated using alternative techniques, namely,
  - Gum elastic bougie,
  - Laryngeal mask airway (e.g., Fastrach),
  - Videolaryngoscope proven to be helpful in difficult orotracheal intubation (Airtraq or GlideScope),
  - Fibre-optic endoscopy,
  - Rescue percutaneous or surgical transtracheal oxygenation.
- Occurrence of complications:
  - Broken teeth,
  - Aspiration of gastric content,
  - Oesophageal intubation,
  - Severe desaturation (SpO₂<90%).
Severe hypotension (systolic blood pressure <90 mm Hg),
- Cardiac arrest.

Variables reflecting morbidity:
- Duration of mechanical ventilation,
- Duration of ICU stay,
- Duration of hospital stay,
- ICU mortality,
- Day-28 mortality.

Participant timeline
The participant timeline is described in table 2.

Sample size
On the basis of previous data, we expect first-pass ETI to be successful in 65% of patients in the Macintosh group. Assuming that using McGrath MAC increases this proportion to 80%, with α set at 5% and β at 10%, 185 patients are needed in each group, that is, 370 patients in all.

Recruitment
Patient inclusion started in June 2015 in seven French ICUs. Enrolment is ongoing. As of 11 August 2015, 111 patients had been included. Recruitment-rate enhancing strategies were deemed unnecessary, an opinion borne out by the higher-than-anticipated recruitment rate so far.

METHODS: ASSIGNMENT OF INTERVENTIONS
Allocation
Randomisation is centralised, web-based and accessible 24 h a day. The randomization scheme is balanced (1:1) and stratified by centre and intubator status, characterised as expert or non-expert. An expert intubator is defined as a doctor who has either worked in ICUs for at least 5 years or has worked in ICUs for at least 1 year after receiving at least 2 years of training in anaesthesia. All intubators who do not meet these criteria are classified as non-experts. Details on the intubators will be recorded in the eCRF, notably resident/junior/fellow/senior status and specialty of residency training if appropriate (anaesthesia; emergency department; other).

Sequence generation
The randomisation sequence was generated by a statistician working at the Clinical Research Unit and not involved in patient recruitment. Randomisation was performed in blocks. The software used to collect the data in the eCRFs automatically allocates the patients, thereby ensuring concealment. In each ICU, the physicians and a clinical research nurse and/or clinical research assistant screen the patients around the clock and include those who are eligible for the study.

Blinding
Blinding of healthcare workers and patients (despite the sedation) to the type of laryngoscopy device is not feasible. However, the primary outcome is assessed on the basis of an objective capnography criterion.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS
Data collection and management
The study data are recorded in a web-based eCRF. They are extracted from the medical records of each patient (source data) by the ICU staff. The data manager, in cooperation with the coordinating investigator, establishes the trial database by exporting data from the eCRFs. Any protocol deviations are recorded in either the eCRF or the medical records; both are checked by a clinical research assistant to ensure that all protocol deviations and adverse events are in the database.

Statistical methods
Statistical analysis
A predefined statistical analysis plan will be followed, using SAS software V9.3 (Cary, North Carolina, USA), with the intent-to-treat approach. The statistical analysis will incorporate all the elements required by the

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D, day; ICU, intensive care unit.
CONSORT statement for non-pharmacological interventions.

Description of the patient groups at baseline
The baseline features of the overall population and of each group will be described, using n (%) for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables. No statistical test will be performed to compare the two groups at baseline.

Analysis of the primary outcome
The proportion of patients with successful first-pass ETI will be compared between the two groups using a generalised mixed model to take the stratification factors into account. A sensitivity analysis based on the MACOCHA score for predicting difficult intubation will be carried out.

Analysis of secondary outcomes
Secondary outcomes will be analysed using generalised mixed models (linear or logistic depending on the variable type). These models will allow us to take into account the stratification of the randomisation scheme on centre (considered to have random effects) and operator experience (considered to have a fixed effect).

For all statistical tests, p values of 0.05 or less will be taken to indicate a significant difference.

Subgroup analysis
We will perform a separate analysis of patients with difficult intubation, defined as three or more laryngoscopies and/or a total ETI duration longer than 10 min.

METHODS: MONITORING
Data monitoring
Before the start of patient recruitment, all physicians and other healthcare workers in the seven participating ICUs attended formal training sessions on the study protocol and data collection in the eCRF. All documents required for the study are available in each ICU. The eCRF is a secure, interactive, web-response system available at each study centre, provided and managed by the biometrics unit of the Nantes University Hospital (Nantes, France). In each participating ICU, the physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data in the eCRFs.

The principal investigators meet with the ICU teams to discuss any problems with data collection and protocol compliance and to evaluate study progress.

According to French law, the eCRF and creation of the database were approved by the appropriate committees (CCTIRS, Comité Consultatif sur le Traitement de l’Information en matière de Recherche dans le domaine de la Santé, N° MMS/VCS/AR1412251, on 16 February 2015).

Harms
The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with the type of laryngoscope used. According to French law, since the strategies used in both study arms are classified as standard care, no specific reporting procedure for unexpected serious adverse events is planned.

Auditing
The Clinical Research Unit of the La Roche-sur-Yon Hospital reviews the screening forms and clinical data at regular intervals.

ETHICS AND DISSEMINATION
Research ethics approval
The trial is conducted in compliance with the current version of the Declaration of Helsinki and Good Clinical Practice guidelines. The research project was approved by the appropriate Ethics Committee for the Protection of Patients (CPP Ouest 2) in Angers, France, on 18 July 2014 (registration number 2014-A00674-43).

Consent or assent
According to French law, since the strategies used in both study groups are considered components of standard care, there is no requirement for consent. Nevertheless, information of the patient or next of kin is required. The patient or next of kin confirms in writing that he/she has received this information. If no next of kin can be contacted during the screening for the study, trial inclusion is conducted as an emergency procedure by the ICU physician, in compliance with French law. Patients who regain consciousness are informed about the trial as soon as possible.

A patient may leave the trial at any time if the person informed about the study (patient or next of kin) is unwilling to continue in the trial. Data from patients who request full withdrawal will not be taken into account in the analysis.

Confidentiality
The study data will be handled as requested by the French Data Protection Authority (CNIL, Commission Nationale de l'Informatique et des Libertés). All original records will be kept on file at the trial sites or coordinating data managing centre for 15 years. The cleaned electronic trial database file will be anonymised and kept on file for 15 years.

Declaration of interests
None of the authors has any financial or other competing interests in relation to this study.
Aircraft Medical Limited, which produces the McGrath MAC videolaryngoscope, had no role in the design of this study and will have no role in its conduct; data collection, analysis or interpretation; or decision to submit the results for publication.

DISCUSSION

To the best of our knowledge, the MACMAN trial is the first randomised multicentre study of videolaryngoscopy for ETI in ICU patients. Previous studies of this strategy had several weaknesses, including the use of a before-after design or patient recruitment at a single centre. Moreover, most of these studies had no formal ETI protocol designed to limit bias due to variations in anaesthesia induction and/or preoxygenation. Also, operator experience was not usually taken into account.

The MACMAN trial has an open-label design, as blinding to the type of laryngoscope used is not feasible. However, the main outcome measure is objective: it is the presence of an inflection on the expired capnography curve, indicating that the tube is in the trachea. ETI duration was the primary outcome measure in many studies. However, ETI duration measurement may lack reliability, as the start and end may be challenging to pinpoint. Other studies used the glottis view quality. However, obtaining a good view does not necessarily translate into successful ETI, and scoring of the view of the glottis is somewhat subjective. In addition, given the low frequency of serious complications, detecting a statistically significant difference in this variable would have required a very large sample size. Moreover, several studies showed a strong correlation between the frequency of complications and the number of laryngoscopy attempts. A larger number of attempts translates into a longer duration of ETI and therefore into a higher risk of aspiration and a greater degree of laryngeal oedema, which decreases the effectiveness of facemask ventilation and increases the risk of desaturation during ETI.

In conclusion, if the main hypothesis is confirmed, videolaryngoscopy will become the reference standard for ETI in ICU patients. Expected benefits of this practice are improved patient safety, via decreases in ETI duration and in the frequency of serious complications (episodes of profound hypoxaemia and cardiac arrest). Videolaryngoscopy would also deserve consideration for use outside the ICU, in settings where emergent ETI is often required (emergency rooms and prehospital emergency-care units) and is a source of substantial morbidity.

Author affiliations
1Medical-Surgical Intensive Care Unit, District Hospital Centre, La Roche-sur-Yon, France
2Clinical Research Unit, District Hospital Centre, La Roche-sur-Yon, France
3Delegation a la Recherche Clinique et a l’Innovation-CHU Hotel Dieu, Nantes, France

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