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Effect of Bag-Mask Ventilation vs Endotracheal Intubation During Cardiopulmonary Resuscitation on Neurological Outcome After Out-of-Hospital Cardiorespiratory Arrest

A Randomized Clinical Trial

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Key Points

Question

Is bag-mask ventilation noninferior to endotracheal intubation for initial airway management during advanced resuscitation of patients with out-of-hospital cardiac arrest?

Findings

In this randomized clinical trial that included 2043 patients, favorable neurological function at 28 days was present in 4.3% in the bag-mask group vs 4.2% in the endotracheal intubation group, a difference that did not meet the noninferiority margin of 1%.

Meaning

The study findings are inconclusive for noninferiority; further research would be necessary to assess equivalence or superiority.

Abstract

Importance

Bag-mask ventilation (BMV) is a less complex technique than endotracheal intubation (ETI) for airway management during the advanced cardiac life support phase of cardiopulmonary resuscitation of patients with out-of-hospital cardiorespiratory arrest. It has been reported as superior in terms of survival.

Objectives

To assess noninferiority of BMV vs ETI for advanced airway management with regard to survival with favorable neurological function at day 28.

Design, Settings, and Participants

Multicenter randomized clinical trial comparing BMV with ETI in 2043 patients with out-of-hospital cardiorespiratory arrest in France and Belgium. Enrollment occurred from March 9, 2015, to January 2, 2017, and follow-up ended January 26, 2017.

Intervention

Participants were randomized to initial airway management with BMV (n = 1020) or ETI (n = 1023).

Main Outcomes and Measures

The primary outcome was favorable neurological outcome at 28 days defined as cerebral performance category 1 or 2. A noninferiority margin of 1% was chosen. Secondary end points included rate of survival to hospital admission, rate of survival at day 28, rate of return of spontaneous circulation, and ETI and BMV difficulty or failure.

Results

Among 2043 patients who were randomized (mean age, 64.7 years; 665 women [32%]), 2040 (99.8%) completed the trial. In the intention-to-treat population, favorable functional survival at day 28 was 44 of 1018 patients (4.3%) in the BMV group and 43 of 1022 patients (4.2%) in the ETI group (difference, 0.11% [1-sided 97.5% CI, −1.64% to infinity]; *P* for noninferiority = .11). Survival to hospital admission (294/1018 [28.9%] in the BMV group vs 333/1022 [32.6%] in the ETI group; difference, −3.7% [95% CI, −7.7% to 0.3%]) and global survival at day 28 (55/1018 [5.4%] in the BMV group vs 54/1022 [5.3%] in the ETI group; difference, 0.1% [95% CI, −1.8% to 2.1%]) were not significantly different. Complications included difficult airway management (186/1027 [18.1%] in the BMV group vs 134/996 [13.4%] in the ETI group; difference, 4.7% [95% CI, 1.5% to 7.9%]; *P* = .004), failure (69/1028 [6.7%] in the BMV group vs 21/996 [2.1%] in the ETI group; difference, 4.6% [95% CI, 2.8% to 6.4%]; *P* < .001), and regurgitation of gastric content (156/1027 [15.2%] in the BMV group vs 75/999 [7.5%] in the ETI group; difference, 7.7% [95% CI, 4.9% to 10.4%]; *P* < .001).

Conclusions and Relevance

Among patients with out-of-hospital cardiorespiratory arrest, the use of BMV compared with ETI failed to demonstrate noninferiority or inferiority for survival with favorable 28-day neurological function, an inconclusive result. A determination of equivalence or superiority between these techniques requires further research.

Trial Registration

clinicaltrials.gov Identifier: NCT02327026

Introduction

The preference for certain techniques recommended by the advanced cardiac life support (ACLS) course for the patient in cardiac arrest is subject to debate. In particular, airway management by endotracheal intubation (ETI) during cardiopulmonary resuscitation (CPR) of patients with out-of-hospital cardiorespiratory arrest (OHCA) is currently contested. Several recent studies, encompassing a great number of patients, have identified a significant association between ETI during CPR and increased mortality. This association also occurs in patients experiencing cardiac arrest in the hospital and among children. Even with large numbers of patients, all of these studies have been retrospective and dependent on large registries. Other retrospective studies, with smaller patient populations, have found a beneficial association with ETI. Recent international norms have not provided a clear recommendation on the choice of bag-mask ventilation (BMV) vs ETI. Ventilation by mask is purported to possess certain advantages, namely, being easier to initiate, interfering less with cardiac massage, and appearing to be associated with few significant complications.

As a consequence of these conflicting data, there has been interest in a randomized study investigating the presence of a link between choice of ventilation technique and survival after CPR. The purpose of this study was to compare BMV and ETI in the treatment of patients with OHCA. The hypothesis was that BMV was not inferior to ETI with respect to 28-day favorable neurological outcome.

Methods

Study Design

Detailed trial protocol and statistical analysis plan are available in Supplement 1. This study was a randomized, parallel-group, noninferiority, 2-country (Belgium and France), multicenter, parallel-group trial comparing the efficacy of BMV vs ETI for advanced airway management in patients with OHCA. This study, carried out between March 9, 2015, and January 2, 2017, involved 20 prehospital emergency medical services (EMS) centers: 15 in France and 5 in Belgium. The follow-up was completed on January 26, 2017. These centers are ambulance base stations equipped with 1 or more

mobile intensive care units, consisting of an ambulance driver, a nurse, and an emergency physician as the minimum team. All EMS personnel included in this study have experience conducting randomized trials with OHCA. French and Belgian out-of-hospital medical systems are 2-tiered EMS response systems with ACLS responders, including trained emergency physicians attending the scene by ambulance. A detailed description of the emergency medical system in France has been previously published. This study was approved by both French and Belgian institutional review boards. In accordance with French and Belgian laws, the boards waived the requirement for obtaining informed consent from patients because of the emergency setting of the research; however, deferred consent of the patient or relatives was required.

Randomization was stratified by center. A computerized random number generator created the randomization list (1:1) in blocks of random size (4 to 8) to ensure balanced distribution of the treatment groups at any time. Group assignments were sent in sealed envelopes to the study centers.

Patient Population

Patients were enrolled over 22 months, from March 9, 2015, to January 2, 2017. The trial included adults aged 18 years or older with out-of-hospital cardiac arrest who received resuscitation performed by clinicians from participating centers. Patients who met any of the following criteria were excluded from the study: suspected massive aspiration before resuscitation, presence of a do-not-resuscitate order, known pregnancy, and imprisonment.

Study Intervention

Out-of-Hospital Period

This period started at the time of randomization and was completed on hospital admission or when death was pronounced at the scene. On arrival of the medical team at the scene, and after verification of participants' eligibility, patients were enrolled in the study and randomly assigned to either initial BMV or ETI. Patients assigned to the intervention group were to receive BMV as advanced airway management by the medical team during CPR (ACLS). Emergency physicians supervise airway management; they perform ETI and can intervene at any time during the airway procedure.

In case of return of spontaneous circulation, the patient was intubated in the out-of-hospital setting. If standard BMV was impossible, or in case of massive regurgitation of gastric contents during ventilation, ETI of the included patient was the rescue procedure. Patients assigned to the control group were to receive ETI during CPR by the medical team. If standard laryngoscopy-assisted intubation was difficult or impossible, a standardized procedure was recommended, including bougie placement, laryngeal mask airway, and video-assisted laryngoscopy, in agreement with French consensus guidelines on difficult airway management. In instances where the primary rescuers (ie, firefighters) arrived at the scene before the medical team, ventilation with the bag mask was performed as part of basic life support.

During the out-of-hospital phase, patients were resuscitated according to international recommendations including a chest compression to breath ratio of 30:2 before ETI attempt and attention to ensure continuous compressions. The emergency physicians working in the prehospital medical teams were all fully trained attending physicians with experience in ACLS and airway management during their regular practice. When ETI was performed during ACLS, unsynchronized mechanical ventilation was initiated, with avoidance of hyperventilation. Patients were transported to the hospital only if they were successfully resuscitated (ie, stable return of spontaneous circulation [ROSC]) at the scene. A 28-day follow-up was performed within the window of 28 to 35 days after resuscitation. Depending on the patient's clinical status, follow-up was performed during a clinic appointment, through contact by telephone or mail with the patient, a family member, legal representative, or family physician or directly in the hospital where possible.

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In-hospital Period This period started at the time of hospital admission and terminated at the time of hospital discharge. No procedures or treatments relevant to the research protocol occurred during hospitalization. If the patient's condition improved during hospitalization, the investigator was required to inform the patient about his or her enrollment in the study. Data collected during this period were death from any cause and vital status at day 28.

Outcomes

The primary end point was survival at day 28 with favorable neurological function, defined as Glasgow-Pittsburgh Cerebral Performance Categories (CPCs) of 2 or less. Collection of this outcome was by blinded assessors. Secondary study end points included rate of survival to hospital admission, rate of survival at 28 days (irrespective of CPC), rate of ROSC, intubation difficulty assessed by the Intubation Difficulty Scale score, difficult intubation (defined by Intubation Difficulty Scale score >5), BMV difficulty assessed by a visual analog scale ranging from 0 mm to 100 mm and by the Han mask ventilation classification, and rate of BMV or ETI failure. Complications related to ETI or BMV were also collected, in particular, the rate of regurgitation of gastric contents. Regurgitation was recorded as an event when direct visualization by the operator of newly regurgitated gastric contents below the glottis (ETI group) or through the mask (BMV group) occurred. Chest compression fraction (defined as the proportion of each minute during which compressions were given) and number of pauses lasting more than 2 seconds were monitored and recorded in one investigative center (Center No. 5: Saint Pierre) for 15 minutes or less of CPR or until ROSC. These parameters were automatically registered by the Corpuls3 monitor/defibrillator used by this center (Corpuls Inc).

Statistical Analysis

Hypotheses for sample size calculations integrated the results of 2 large observational studies of this subject. A study by Hasegawa et al based on a registry of 650 000 patients reported a survival rate with favorable neurological function in the BMV group of 3%, associated with an odds ratio in favor of BMV equal to 0.38 (95% CI, 0.36-0.39) vs 1.1% survival with ETI. Similarly, the study by Gueugniaud et al reported a rate of only 2% for this outcome with ETI. Sample size calculation was therefore based on presumed true rates for the primary end points of 3% and 2%, respectively. We defined a priori a noninferiority margin of 1% (absolute value) because it was an increase of risk (both in absolute and relative terms) lower than most of the noninferiority margins used in studies with primary end points such as death and/or severe morbidity. In addition, using a putative placebo approach similar to that described by Mulla et al, considering a percentage of patients surviving without severe sequelae to be 2% with ETI and null in absence of resuscitation, it can be considered that at least 50% of that reference treatment effect would be preserved with this choice. Using these hypotheses, 956 patients per group would allow an 80% power to demonstrate noninferiority using a method based on a 95% 2-sided CI (based on 5000 simulations using the Newcomb-Wilson score method). Thus, it was necessary to recruit a total of 2000 patients.

The primary aim of the trial was to assess noninferiority of the bag mask vs ETI, with a rate of survival with favorable neurological function (π) as the primary end point. Analysis of the primary end point was carried out by calculating the 95% 2-sided CI of the difference: $\pi_{bag} - \pi_{tracheal}$. The conclusion of noninferiority would be accepted if the lower limit of this CI was higher than −1%. In the event of demonstration of noninferiority, a test of difference would be carried out. Because it was a noninferiority trial, the main analysis was based on both the intent-to-treat population (ITT) of all patients randomized (irrespective of which study treatment was given or whether study treatment was adequately received) and the per-protocol analysis of all patients randomized and treated without major protocol violations or deviations. A safety population was defined as all treated patients according to the treatment actually received. In these analyses, adverse events related to patients for whom intubation was attempted but was not successful were related to ETI.

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The secondary end points were tested for superiority. For all secondary criteria expressed as rates, the χ^2 test on proportions was used and the corresponding 95% CI on their odds ratio and differences were also calculated. For quantitative secondary end points, the *t* test or Mann-Whitney test were used according to their gaussian or nongaussian statistical distribution. The significance threshold was 2-sided $P = .05$ without adjustment for multiplicity. Because of this, secondary analyses should be considered exploratory.

Several post-hoc analyses were also performed: (1) an estimate of the risk difference and its 97.5% CI using a hierarchical modeling that included centers as a random effect, (2) comparison of the chest compression fraction (CCF) and the number of pauses greater than 2 seconds during CPR between the 2 groups in center No. 5, (3) an ITT analysis by excluding patients for whom CPR and other procedures were prolonged and modified beyond standard resuscitation by extracorporeal membrane oxygenation–CPR and organ donation after circulatory determination of death, and (4) an ITT analysis by considering in the ETI group patients intubated after BMV and before ROSC.

All analyses were carried out using SAS Software version 9.4 (SAS Institute).

Results

Baseline Characteristics

A total of 2043 patients were enrolled during the study. Of those, 1020 patients were enrolled in the BMV group and 1023 in the ETI group. The ITT population was composed of 2040 patients (Figure). The number of inclusions for each investigator center is detailed in eTable 1 in Supplement 2. The population and per-protocol analysis was composed of 995 patients in the BMV group and 943 patients in the ETI group (see reasons for exclusions in the Figure). The safety population was composed of 2027 patients (1028 in the BMV group and 999 in the ETI group; Figure). Patient characteristics and the process of resuscitation were well balanced between the 2 groups except for age and history of psychiatric disorder (Table 1). None of the observed differences appeared to be clinically significant.

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Figure.
Flow Chart of Patient Inclusion

The number of patients assessed for eligibility was not available. BMV indicates bag-mask ventilation; ETI, endotracheal intubation; ITT, intention to treat; PP, per protocol; and ROSC, return of spontaneous circulation.

[a]Several reasons may be present for the same patient.

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Table 1.

Characteristics of Patients Included in the ITT Analysis and Cardiac Arrest Management

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Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BMV, bag-mask ventilation; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; EMS, emergency medical services; ETI, endotracheal intubation; IQR, interquartile range; ITT, intention-to-treat.

[a]Activity limitations: good health = previous good health, no functional limitations; moderate limitation of activity = mild-to-moderate limitation of activity because of a chronic medical problem; chronic disease = chronic disease causing serious but not incapacitating limitation of activity; and severe restriction of activity = severe restriction of activity due to disease, including being bedridden or institutionalized because of illness.
[b]No-flow duration: time delay between collapse and commencement of basic life support.
[c]Uncontrolled donation means kidney grafts retrieval from non–heart-beating donor after out-of-hospital cardiac arrest.

Primary Outcome

In the ITT population, favorable functional survival (ie, CPC 1-2) in the 2 groups at day 28 were 44 of 1018 patients (4.3%) in the BMV group and 43 of 1022 patients (4.2%) in the ETI group (difference, 0.11% [1-sided 97.5% CI, −1.64% to infinity]; *P* for noninferiority = .11). The lower limit of the confidence interval was greater than the threshold of noninferiority, thus noninferiority was not demonstrated. Very similar estimates were obtained using a hierarchical modeling including center as a random effect (difference, 0.05% [1-sided 97.5% CI, −1.70% to infinity]). This result was consistent in the per-protocol population: 4.3% vs 4.2% in the BMV and ETI groups, respectively (difference, 0.08% [1-sided 97.5% CI, −1.74% to infinity]; *P* for noninferiority = .12).

Secondary Outcomes

In ITT analysis, the rate of ROSC was significantly greater in the ETI group (397/1022 [38.9%]) vs in the BMV group (348/1018 [34.2%]) (difference, −4.7% [95% CI, −8.8% to −0.5%]; *P* = .03). The survival to hospital admission and survival at day 28 were not, however, significantly different between the 2 groups (BMV vs ETI: 294/1018 [28.9%] vs 333/1022 [32.6%]; difference, −3.7% [95% CI, −7.7% to 0.3%] and 55/1018 [5.4%] vs 54/1022 [5.3%]; difference, 0.1% [95% CI, −1.8% to 2.1%]) (Table 2). These results were not modified in the per-protocol analysis (Table 2)

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Table 2.

Secondary Outcomes in Patients Included in the Study

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Abbreviations: BMV, bag-mask ventilation; CPCs, Cerebral Performance Categories; ETI, endotracheal intubation.

[a]*P* values were calculated by using χ^2 test or Fisher exact test.
[b]CPCs 1 and 2 were counted as success when coding the primary outcome.

Adverse Events Analysis

Complications that were significantly more frequent in the BMV group compared with the ETI group included airway management difficulty (186/1027 [18.1%] in the BMV group vs 134/996 [13.4%] in the ETI group; difference, 4.7% [95% CI, 1.5% to 7.9%]; $P = .004$), failure (69/1028 [6.7%] in the BMV group vs 21/996 [2.1%] in the ETI group; difference, 4.6% [95% CI, 2.8% to 6.4%]; $P < .001$), and regurgitation of gastric content (156/1027 [15.2%] in the BMV group vs 75/999 [7.5%] in the ETI group; difference, 7.7% [95% CI, 4.9% to 10.4%]; $P < .001$) (Table 3).

Table 3.

Airway Management Adverse Events Analysis

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Abbreviations: BMV, bag-mask ventilation; ETI, endotracheal intubation; IQR, interquartile range; NA, not applicable; VAS, visual analog scale.

[a]*P* values were calculated by using χ^2 test or Fisher exact test.
[b]BMV difficulty was recorded by the operator after termination of resuscitation. The BMV VAS ranges from 0 (ventilation without difficulty) to 100 (maximum ventilation difficulty).
[c]ETI difficulty is defined by Intubation Difficulty Scale score greater than 5. Intubation Difficulty Scale score ranged from 0 (intubation without difficulty) to infinity. A value greater than 5 defines difficult intubation. BMV difficulty was defined by Han scale score greater than 2 (grade 1: easy mask, grade 2: difficult mask requiring an oral airway or other adjuvant, grade 3: very difficult mask ventilation requiring 2 practitioners, and grade 4: unable to mask ventilate).
[d]Mainstem intubation was detected in the field by auscultation.
[e]There were no unrecognized esophageal intubations.

Post-Hoc Analyses

Analysis was performed of 115 patients (BMV group = 56 patients; ETI group = 59 patients) from center No. 5 to determine CCF and the number of pauses greater than 2 seconds during CPR in the 2 groups, finding no significant difference between the 2 groups concerning CCF (87% in ETI group vs 86% in the BMV group; difference, −1% [95% CI −4% to 2%]; $P = .70$), but a significantly greater number of pauses longer than 2 seconds in the BMV group (27 in the BMV group vs 16 in the ETI group; difference, 11 seconds [95% CI, 7 to 15]; $P < .001$).

The results were comparable for the 2 other post hoc analyses: (1) after exclusion of patients for whom CPR and other procedures were prolonged and modified beyond standard resuscitation by extracorporeal membrane oxygenation–CPR and organ donation after circulatory determination of death (n = 91) and (2) after exclusion of patients intubated after BMV and before ROSC considered in the ETI group (n = 155) (data detailed in eTable 2 in Supplement 2).

Discussion

In this randomized clinical trial of patients with out-of-hospital cardiorespiratory arrest, the use of BMV compared with ETI failed to demonstrate noninferiority or inferiority for survival with favorable 28-day neurological function, an inconclusive result.

International recommendations recognize inherent weaknesses in registry studies. Although studies have suggested better survival for BMV, these studies may have been prone to biases. Despite approaches to control confounding or to study matched cohorts, intubated patients may be more severely ill, resulting in a more aggressive approach to resuscitation. As a result, US, European, and International Liaison Committee on Resuscitation synthesis documents recommend both intubation and ventilation by mask as airway interventions in the course of cardiac arrest (class IIb).

A large Japanese observational study of 649 359 patients demonstrated a significant decrease in favorable functional survival associated with tracheal intubation vs ventilation by bag mask (1.1% vs 2.9%). These results have been confirmed in other registry studies concerning out-of-hospital cardiac arrest, in-hospital cardiac arrest, and cardiac arrests among children. The results were not modified after adjustment of confounding factors, analyses using multivariable logistic regression models, tests of sensitivity, or propensity scores. However, other observational studies with fewer patients have found opposite results.

The present study aimed to clarify this question, though providing data on both efficacy and rate of adverse events based on the first direct comparison between these 2 techniques via a randomized clinical trial.

Demonstration of noninferiority of BMV might be sufficient to adopt this technique as the primary airway strategy in patients with OHCA because this approach has several advantages, including more straightforward implementation and potentially fewer complications. A test of superiority would have been performed had noninferiority been demonstrated. This study was inconclusive regarding the main criterion as noninferiority could not be demonstrated and it may have been underpowered. The sample calculation was based on an assumption of greater likelihood of favorable neurological outcome in the BMV group compared with the ETI group. Instead, the point estimates in this trial were close (4.3% vs 4.2%), which may have contributed to underpowering. An assumption of equal outcomes between the 2 groups might have required a much larger sample size to demonstrate noninferiority.

Although there was a significantly higher rate of ROSC in the ETI group vs the BMV group, overall 28-day survival was not different. This may be related to differences in ventilation-associated complications (hyperoxia, overventilation, and hypotension) between the 2 randomized groups and these factors would need to be considered in future trials.

The difficulties with ETI in the present study are similar to those previously reported. The negative interaction between the quality of cardiac massage and the performance of ETI is known to affect favorable functional survival. ETI has been linked to significant interruptions in cardiac massage. However, a large, randomized study found no effect on survival caused by short interruptions of cardiac massage when 2 manual ventilations occurred between cycles of cardiac massage. In this trial, the post-hoc analysis of a small subgroup of 115 patients found no significant difference in CCF

between the 2 randomized groups. The greater number of pauses longer than 2 seconds observed in the BMV group was likely the consequence of cardiac massage interrupted by manual ventilation during CPR, with a rhythm of 30:2.

A concern about ETI as standard airway management in OCHA is the experience and skill required by the operator for successful intubation. International recommendations suggest that intubation should only be carried out by advanced operators. In this study, it is possible that the physician in the out-of-hospital team had a higher level of competence compared with paramedic teams from other European and non-European countries. However, the incidence of difficult intubation between paramedics and medicalized European prehospital teams does not appear to be significantly different. In France, the difficult intubation rate in the out-of-hospital setting has been reported to be between 9% and 11% and is comparable in this study. In a multicenter trial carried out in the United States, including 1941 patients, among whom 1272 were in cardiac arrest, the authors found a success rate for intubation of 91.8% after fewer than 3 attempts, the incidence of difficult intubation thus being 9.2%. Thus, the staffing of out-of-hospital teams was not likely to be a determining factor in explaining these results.

Another advantage of this direct randomized comparison of the 2 techniques is that it allows clear discrimination of their adverse events. BMV was associated with a notable rate of complications and failure. Although BMV is seldom a topic of research, criteria for difficult mask ventilation have been described, and several studies have identified complications, such as pulmonary aspiration and gastric distention. The higher incidence of regurgitation of gastric contents in the BMV group supports these few studies linking BMV with risk for the patient.

In the present trial, a higher incidence of failure of the BMV technique, compared with ETI, is also noteworthy. The rate of difficult BMV or BMV failure was higher than in observational studies in general anesthesia and may be explained by the emergency conditions and the absence of preexisting airway evaluation. On the other hand, in the BMV group, the ease to use the rescue technique (ie, tracheal intubation) may have contributed to an inflated rate of BMV failure. Thus, the BMV technique can still be appropriately used to manage the airway during CPR.

Limitations

This study has several limitations. First, the presence of a physician in the ambulance team may make the results of this study less relevant for designing strategies for US-based EMS systems, where the number and training of available clinicians at the out-of-hospital resuscitation scene clearly differ. However, airway management during CPR in patients with OHCA, and the choice of the best-suited approach, is common to all systems, particularly in countries where paramedics also perform tracheal intubation regularly.

Second, the use of ETI in the BMV group either after ROSC or when difficulty with airway management was encountered may question the BMV-only strategy in the intervention group. However, post-hoc analysis with removal of patients with protocol violations did not change results in terms of survival. After successful resuscitation of patients included in the BMV group, it is expected that all these patients were intubated (in the out-of-hospital setting or in the hospital). The principal aim of this trial was to identify the better airway management strategy in ACLS of patients with OHCA rather than post-ROSC care.

Third, this trial did not include comparison of inpatient management after cardiac arrest, which could vary considerably. However, because this study was randomized, the 2 groups should be comparable in terms of in-hospital management.

Fourth, secondary analyses in this study should be interpreted as exploratory because type 1 error due to multiple comparisons was not addressed.

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Conclusions

Among patients with OHCA, the use of BMV compared with ETI failed to demonstrate noninferiority or inferiority for survival with favorable 28-day neurological function, an inconclusive result. A determination of equivalence or superiority between these techniques requires further research.

Notes

Supplement 1.

Trial Protocol

Click here for additional data file. (3.3M, pdf)

Supplement 2.

eTable 1. Number of Cases That Each Investigator Centre Contributed

eTable 2. Post-Hoc Analyses

Click here for additional data file. (86K, pdf)

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