1.0 Abstract

Title

A prospective, open-label, multicenter, post marketing, observational study to investigate the effectiveness of Sevoflurane anaesthesia in difficult-to-intubate Egyptian patients.

Keywords

Sevoflurane

Anaesthesia

Difficult to intubate (DTI)

Rationale and Background

Tracheal intubation is the placement of a flexible plastic tube into the trachea (windpipe) to maintain an open airway and provide oxygenation either manually or by mechanical ventilation. Certain drugs may also be administered through the tube. Tracheal intubation is an invasive process and is usually carried out under general anesthesia to facilitate Lung ventilation and to prevent the potential of asphyxiation or airway obstruction.[1] Moreover, patients are considered difficult to intubate, where tracheal intubation requiring multiple intubation attempts in the presence or absence of tracheal pathology; or as assessed as class three or class four by the Mallampati classification which correlates tongue size to pharyngeal size.[2,3] There are many reasons that contribute to difficult intubation which include, but are not limited to, edentulism, anatomic micrognathia or macroglossia, neck or face trauma, burns with airway edema, infections (retropharyngeal abscess, submandibular abscess, epiglottitis, or croup), neoplasms, rheumatoid arthritis, diabetes mellitus, waxy skin, decreased functional residual capacity, airway closure in supine position, morbid obesity (BMI > 35), airway edema, and laryngospasm.[4-11] Difficult tracheal intubation accounts for 17% of the respiratory-related injuries and results in significant morbidity

and mortality. Twenty-eight percent (28%) of all anaesthesia-related deaths are secondary to the inability to mask ventilate or intubate.[12,13] Identifying the reason for difficult intubation before inducing anaesthesia allows for optimum preparation and the right choice of procedure.[2]

Induction of anesthesia via Inhalation is one of the standard methods for the management of difficult airways. The use of sevoflurane (which is a nonflammable liquid inhalational anesthetic agent administered by vaporization) has been shown to be the least irritating of all the existing agents, which makes sevoflurane a suitable choice of inhalational agent for both adult and pediatric populations.[14-20] However, data on using sevoflurane in difficult-to-intubate Egyptian patients is incomplete, especially due to high obesity rates in Egypt, particularly among women. The overall prevalence of central obesity among Egyptian adults, according to waist circumference indicator and waist-hip ratio were 24.1% and 28.7% respectively.[9-11] Moreover, the average BMI among mothers of young children has increased from 26.9 in 1992 to 28.6 in 2005.[14]

Thus studying the effectiveness of sevoflurane in difficult-to-intubate, non-obstetric Egyptian patients undergoing surgery is deemed important to confirm the efficacy and safety of sevoflurane.

Research Question and Objectives

The purpose of this study was to record the effectiveness of sevoflurane in intubation in Egyptian, non-obstetric patients undergoing surgery who suffer from suspected difficult intubation in regards to the rate of intubation success.

<u>The Primary Endpoint</u>

The percentage of clinical success among enrolled per-protocol patients (A success was defined as intubation achieved in < 4 attempts).

The Secondary Endpoints

- Descriptive analysis (mean/average, SD, SE) of the duration of induction (in seconds) was defined as the time required reaching a Ramsay score of 5 from start of induction.
- The percentage of the preoperative Mallampati scores to identify the degree of difficult intubation.
- Descriptive analysis (mean/average, SD, SE) of the duration of intubation procedure (in minutes) was defined as the time from intubation start to the completion of the intubation process (from tube introduction to $PETCO_2$).
- The percentage of patients who experienced complications resulting from intubation procedure (including, but not limited to bleeding, salivating, lung aspiration).
- The percentage of patients who experienced difficulties related to the use of sevoflurane (including, but not limited to vocal cords adduction, coughing, movements, apnea episodes).
- Descriptive analysis (mean/average, SD, SE) of intubation attempts.
- Safety/tolerability analysis was done through calculating incidence of Serious Adverse Events (SAE) in frequency tables in relation to its severity (mild, moderate, severe and serious/life-threatening) and grade.

Study Design

This study was a multicenter, prospective, observational study.

Setting

Since all data was collected during the perioperative period, the study was completed with 1 visit by the patient for his/her procedure.

Subjects and Study Size, Including Dropouts

Previous international studies showed that the percentage of patients who achieved successful intubation after sevoflurane use in anesthesia induction was 90%.[18-20] Therefore, a sample size of 97 patients was sufficient to estimate the percentage, if

patients had a successful intubation with a precision of 6% and a confidence interval of 95%.

Criteria

Inclusion Criteria:

1. Male or non-pregnant female over 18 years who were undergoing surgery and using sevoflurane as the anesthetic agent with Mallampati score III or IV.
2. Patients with at least one of the below criteria:
    1) Anatomic
        - micrognathia – small mandible
        - macroglossia – large tongue
        - short or fixed neck
        - anterior vocal cords
    2) Trauma – neck or face
    3) Burns – airway edema
    4) Infections with edema
        - retropharyngeal abscess
        - submandibular abscess
        - epiglottitis
        - laryngotracheobronchitis (croup)
    5) Neoplasms; e.g., laryngeal tumors
    6) Rheumatoid arthritis – TMJ immobility
    7) Diabetes mellitus
    8) Waxy skin – palm test

9) Decreased FRC – rapid desaturation (due to displaced diaphragm, increased closing capacity and small airway closure, increased oxygen consumption)
10) Airway closure in supine position
11) Morbid obesity (BMI > 35)
12) Airway edema
13) Laryngospasm
14) Edentulous patients – indent cheeks.

3. Patients were willing to sign informed consent.

Exclusion Criteria:

1. Patients with current use of opioids and/or narcotic dependent.
2. Patients with known sensitivity to sevoflurane or to other halogenated agents.
3. Patients with known or suspected genetic susceptibility to malignant hyperthermia.
4. Alcohol addictive patients.
5. Patients with renal insufficiency (baseline serum creatinine greater than 1.5 mg/dL).
6. Patient was pregnant or breastfeeding.

Variables and Data Sources

The study included one visit.

At baseline, patients were evaluated for inclusion and exclusion criteria. If eligible for inclusion, informed consent form was signed and the patients' demographic data were recorded as well as their medical history, including completion of renal function tests

and pregnancy test. In the operating room, anesthesia was induced. Sevoflurane was used to induce anesthesia, as previously described, by the treating physician at an appropriate dose according to their best effectiveness as judged by the investigator and in compliance with the drug market authorization and approved product (labeling).

The Ramsay Sedation Scale (RSS) was the first scale to be defined and was designed as a test of arousal. The RSS scores sedation at six different levels, according to how arousal the patient is. It is an intuitively obvious scale and therefore lends itself to universal use, wherever sedative drugs or narcotics are given.

The RSS defines the conscious state from a level 1: the patient is anxious, agitated or restless, through the continuum of sedation to a level 6: the patient is completely unresponsive. Therefore, when an assessment is to be made, the first decision to be made is to note if the patient is awake. If the patient is awake: are they anxious, agitated or restless (RSS 1) or are they calm, co-operative and communicative (RSS 2). If the patient is asleep then a test of reusability (repeat the RSS) needs to be made. If the patient responds quickly to a voice command, this is an RSS 3. If the response is slow, then the patient is assigned a level 4. If the patient does not respond, a stronger stimulus is applied. A louder auditory stimulus or a glabellar (between the eyebrows) tap is enacted. A brisk response to this test of arousal places the patient at a RSS 4. A slow or sluggish response categorizes the patient to an RSS 5. No response at all places the patient at a level 6.[2]

1	Anxious, agitated or restless
2	Calm, co-operative and communicative
3	Response is quick to a voice command
4	Response is slow to a voice command
5	Slow or sluggish response
6	No response at all places the patient

Data Recorded Before Intubation Procedure:

a. Informed consent obtained
b. Demography (Age, Gender, Weight, Height, Race)
c. BMI
d. Reason for suspecting difficult intubation (was summarized using frequency table)
e. Previous concomitant medications within 30 days prior to the start of the study
f. Medical history and Mallampati score

Data Recorded During Intubation Procedure:

- Duration of Induction (time from start of induction to reaching a Ramsay score of 5, in seconds).
- Number of Intubation Attempts following the guidelines of ASA (maximum of three attempts to guard against any patient injury that might happen).
- Whether Intubation was successful following the guidelines of ASA.
- Duration of Intubation procedure (from start of intubation to completion of intubation).
- AE.
- SAE: reported to AbbVie within 24 hours of physician awareness.

Data Recorded After Intubation Procedure:

- Narrative of the anesthesia procedure and the intubation procedure followed by analysis; this narrative was read carefully to see if it included any important information related to adverse events, sevoflurane dose, physician opinion on severity of the case, etc. If the physician's narrative doesn't include any important data, it was determined that no further analysis was necessary.
- Dose(s) used for induction of anesthesia using sevoflurane with a recording of the fresh gas flow rate.

- Any other concomitant treatments given during procedure, the reason for administering such treatments and their doses.
- SAE: reported to AbbVie within 24 hours of physician awareness.

Results

Ninety-seven subjects (ITT) were enrolled in the study and prescribed sevoflurane anesthesia due to an anticipated difficulty in intubation during surgery. One patient was excluded due to protocol violation (with a Mallampati score of II). Accordingly, the per-protocol (PP) study population consisted of 96 patients who were included in the study's demographics and efficacy analysis.

Of the 96 participants, 56.25% were female (n = 42) and 43.75% were male (n = 54), with a mean age of 48.80 ± 15.04 years. The baseline means for weight, height and BMI were 94.63 ± 23.18 kg, 166.31 ± 9.42 cm and 34.65 ± 10.11 kg/m^2, respectively. Out of the 96 evaluable participants, 37 patients (38.5%) were morbidly obese (BMI ≥ $35kg/m^2$), while 59 patients (61.5%) were not (BMI < $35kg/m^2$).

The preoperative Ramsay Sedation Score (RSS) revealed 63 patients (65.6%) with level 1 and 33 patients (34.4%) with level 2, while none of patients were with level 3 prior to sedation.

All the anaesthetized patients underwent surgical procedures. The most frequently witnessed surgeries were total thyroidectomy, cholecystectomy, fix fracture mandible, and lumbar discectomy, constituting 9.4%, 8.3%, 4.2% and 4.2% of patients, respectively.

The clinical success rate of intubation in difficult-intubation patients after induction with sevoflurane was 96.9% (93 patients). The mean duration of anesthesia induction was 220.44 ± 229.52 seconds (3.67 ± 3.83 minutes). Mallampati classification showed that most of patients (n = 90, 93.8%) were classified as class 3, while only five patients (5.2%) were classified as class 4. The mean duration of intubation was

106.14 ± 117.25 seconds (1.77 ± 1.95 minutes). A mean of 1.26 ± 0.51 intubation attempts were carried out on PP study participants.

Regarding the safety profile, 2 nonserious AEs (2.1%) were reported in the ITT study population: one reported case of hypertension, and one patient experienced cough. Both events were considered by the investigator to be related to the intubation procedure, rather than the sevoflurane induction. Moreover, corrective clinical action resulted in the resolution of reported events. No serious adverse events were reported.

Discussion

The main aim of this study was to assess the clinical success in terms of intubation achieved in less than four attempts for patients who were difficult to intubate with a Mallampati score of three or four scheduled for surgery, and for whom their treating physician prescribed sevoflurane as their anaesthetic agent. Ninety-seven patients were recruited, with 96 patients meeting eligibility criteria for participation. The results revealed a high success rate of about 97% with high safety profile of 97.9%.

Marketing Authorisation Holder(s)

AbbVie UK

Names and Affiliations of Principal Investigators