

PROTOCOL: Search and identification of studies

Awareness and bispectral index (BIS) monitoring in mechanically ventilated patients in the emergency department and intensive care unit: a systematic review protocol
PROSPERO Registration Number: 147236

Background: From operating room (OR) data, the incidence of awareness with explicit recall is approximately 1-2 cases/1,000. However, in patients given only intravenous anesthesia, that incidence approaches 1%. This is significant because mechanically ventilated patients in other domains, such as the emergency department (ED) and intensive care unit (ICU) are exclusively managed with intravenous (not inhaled) analgesics and sedatives. Risk factors for awareness include: 1) under-dosing of anesthesia; 2) neuromuscular blocker use; and 3) a lack of protocolled monitoring of sedation depth. Therefore, evidence-based recommendations regarding mechanically ventilated patients in the OR endorse avoiding or minimizing neuromuscular blockers, and objective brain monitoring [i.e. with Bispectral index (BIS)] as a means to reduce the incidence of awareness in patients receiving an intravenous anesthetic approach

In contrast to the recommendations above, mechanically ventilated patients in the ED have been historically managed in a way that predisposes them to experience awareness. Critically ill ED patients requiring mechanical ventilation *only* receive intravenous medications, and are typically under-dosed. Further, a significant percentage (up to 50%) of ED patients receive no analgesia or sedation after intubation. Approximately 90% of patients receive a neuromuscular blocker for intubation in the ED, and up to 25% receive a long-acting neuromuscular blocker after intubation. In the ED, these paralyzed patients typically receive less analgesia and sedation, lower doses, and in a delayed fashion. These practice patterns are completely discordant to recommendations for reducing the incidence of awareness, and suggest that patients mechanically ventilated in the ED are at higher risk for this complication.

Case reports from the ED confirm the terrifying psychological sequelae that can result from awareness with paralysis. Puller et al. reported that ~25% of patients recalled an intolerable level of distress during rapid sequence intubation (RSI), and ~45% recalled some level of awareness during intubation. Miner et al. reported that 4/26 (15.4%) patients had recall of intubation, three of whom had a visual analog scale of 100 (complete recall). Kimball et al. reported on 5/10 (50%) patients with recall of intubation and Smith et al. reported that 2/34 (5.9%) patients recalled emergent intubation, but did not report location of recall (i.e. ED, ICU, prehospital, ward). Despite the fact that >800,000 patients are mechanically ventilated annually in U.S. ICUs, data regarding awareness with paralysis from the ICU population is also quite sparse. However, there is a concerning discrepancy between the low incidence of awareness in OR patients (1-2/1000) and the reported rates in the ICU (4% - 36%)

There is rationale to suggest that BIS monitoring could reduce the incidence of awareness in mechanically ventilated ED patients. An ICU-based before-after trial demonstrated a reduction in awareness from 18% to 4% with the use of BIS monitoring. Additionally, while routine clinical monitoring of sedation depth using sedation scales such as RASS are important, our data suggests that this is not routinely done in the busy ED environment.

The prior research regarding awareness in mechanically ventilated ED patients is limited for several reasons: 1) publications exist in abstract (i.e. non peer-reviewed) form; 2) case series and convenience (i.e. non-consecutive) sample methodology; 3) non-validated questionnaires to assess awareness (i.e. Likert, visual analog scale, 1-10 scale); 4) small sample size; and 5) a

focus on awareness of the intubation procedure only, as opposed to intubation *and* the post-intubation mechanical ventilation period.

Given the data on post-intubation sedation in the ED, the psychological trauma that results from awareness with paralysis, and the data gaps that exist in awareness reporting outside of the OR, a rigorous evaluation of literature is warranted to assess the burden of awareness outside of the OR before planning future studies

The objectives of this systematic review are to collate the global biomedical literature to determine: 1) the incidence of awareness with paralysis in the ED and ICU; 2) assessment methods/tools used to assess for awareness; 3) BIS monitoring; and 4) reported data on sedative and neuromuscular blockade use in the studies assessing for awareness. Our overarching hypothesis is that that data from the ED and ICU domains is relatively sparse regarding awareness/recall with paralysis and that few studies have rigorously assessed for and reported awareness

Patient/Problem: Critically ill mechanically ventilated patients (ED, ICU, or prehospital)

Intervention: None.

Comparison: Awareness vs. no awareness

Outcomes:

The primary outcome of interest is the incidence of awareness with paralysis. We will also report on recall/memory of events.

The secondary outcomes of interest are the reporting methods used to assess for awareness and how awareness was defined in each study, as well as studies reporting the use of BIS monitoring in mechanically ventilated patients.

Descriptive reporting will also include the use of sedatives and neuromuscular blockers (if reported).

We will also attempt to report outcome differences that exist between patients experiencing awareness vs. not, including post-traumatic stress disorder (PTSD), delirium, and lengths of stay [ventilator, ICU, hospital (measured as total duration or ___-free days)].

Clinical question: What is the incidence of awareness with paralysis in mechanically ventilated patients in the ED, ICU, or prehospital environments?

Do any clinical studies address pre-ICU (pre-hospital, ED) BIS monitoring (or any other interventions) and its potential impact on the incidence of awareness?

Inclusion Criteria	Exclusion Criteria
<p>Any language or publication type, including case series/studies providing necessary data</p> <p>Adults</p> <p>Invasive positive pressure ventilation during study period</p> <p>Outcomes of interest reported: awareness, recall/memories, BIS monitoring. Including large RCTs examining neuromuscular blockers in mechanically ventilated patients (e.g. recently completed ROSE Trial).</p>	<p>Non-human studies</p> <p>Paper = review, correspondence, or editorial</p>

Step 1 (Electronic Search/Relevance Screen):

Lauren Yaeger (trained medical librarian) will conduct an electronic search, as detailed in the fully reproducible search strategy (online supplement for the manuscript).

RDP and WW: Screen title and abstract of manuscripts resulting from electronic search. Keep track of the number of duplicate articles for documentation in Figure 1. If unclear if manuscript meets inclusion by screening title and abstract, look up full manuscript online for a screening review of inclusion/exclusion criteria.

Step 2 (Independent Reviewers' Comparisons):

RDP and WW: Compare their included studies to determine if disagreement exists. If disagreement exists, a third reviewer (BWR, RJS, or BMF), along with the two independent reviewers, will reach consensus.

Step 3 (Full Text Review):

After consensus is reached, full text articles will be obtained and comprehensively reviewed for inclusion. After this comprehensive review, data extraction for the included manuscripts will be performed (RDP) using standardized data collection forms.

Step 4 (Identify Unpublished Data):

RDP: Manually screen reference lists of all included articles from the electronic search.

RDP: Search online for details of clinical trials registration (ClinicalTrials.gov).

RDP, WW, or RJS: Hand search abstracts from: ACEP, SAEM, ATS, CHEST, SCCM, ESICM, International Symposium on Intensive Care and Emergency Medicine, ASA, European Society of Anaesthesiology, International Anesthesia Research Society, and AACN, from 2010 to 2019.

BMF: If unpublished data is found and clarification is needed, contact PI of that study.

Step 5 (Collate the Data):

Transfer data from standardized data collection forms to tables: author, year of publication, study design, number of included patients, population characteristics, awareness data, BIS data, risk of bias, clinical outcomes, and pertinent study-specific comments.

In addition, study quality should be tabled: Cochrane tool for clinical trials, and Newcastle Ottawa Scale for observational studies.

Step 6 (Meta-analysis Screen):

The primary objective is to report the incidence of awareness, an overall rare but devastating complication, and to qualitatively report on the studies that have assessed for it. However, it may be possible to objectively analyze some of the data (as opposed to qualitative reporting

only). Therefore, after the data is collated into table form, it will be assessed for the potential to meta-analyze the data. Factors determining whether meta-analysis is appropriate will be: clinical characteristics and heterogeneity of the studies, clarity of outcomes reporting, study design (s), and presence of bias. If meta-analysis is appropriate, the data will be pooled; heterogeneity (I^2 statistic) and publication bias (funnel plot) will be assessed.

Step 7 (Qualitative Data Description):

After data is collated, descriptive data will be provided for data points such as: study characteristics, study quality, awareness reporting, BIS monitoring, and medications used for sedation