Introduction

Sedation in the intensive care unit (ICU) is part of the treatment strategy in critically ill patients as anxiety and agitation are experienced by more than 70% of ICU patients ***(Carrasco and Cabre, 1994)***. Sedation in the ICU allows for a comfortable and cooperative patient, decreases the levels of anxiety and stress, reduces insomnia and the risk of awareness during stressful interventions, and normalizes metabolism and hemodynamics ***(Blanchard, 2002).*** Sedation is often used to facilitate mechanical ventilation, to suppress gag reflexes related to the tubing system and to treat self-destructive agitation. Finally, sedation has been proposed as a neuroprotective intervention in head-injured patients and in status epileptics ***(Kress et al., 1996)***.

Administration of sedative drugs should aim to keep the patient comfortable, calm and cooperative but easily aroused ***(Tung and Rosenthal, 1995).*** Theoretically the ideal hypnotic should have favorable kinetics that enable rapid onset, easy targeting of sedation and quick offset form sedation. ***).*** An acute withdrawal syndrome following prolonged use of sedative or analgesic drugs has also been reported in ICU patients ***(Cammarano et al., 1998).***

This hypnotic would also have an acceptable adverse effect profile. Under these conditions, the hypnotic is expected

to shorten ICU stay and thus decrease cost, reduce morbidity, and even mortality ***(Blanchard, 2002).***

There is no doubt that sedation may have negative side effects, including an increased risk of venous thrombosis, decreased intestinal motility, hypotension, reduced tissue oxygen extraction capabilities, immunosuppression, failure to recognize cerebral insult (**Schwiekert et al., 2004),** prolonged ICU stay and increased costs ***(Kollef et al., 1998).*** It has become very important that it is not enough to choose the appropriate sedative and right dosing schedule, but also, it is of great importance to monitor and assess the patients level of sedation regularly and to adjust the drug regimen accordingly ***(Tonner et al., 2006).*** However in spite of the difficulties in sedation practice, and adverse effects of commonly used drugs, this does not change the fact that the agitated ICU patient must be treated with sedatives in order to progress to a recovery phase ***(Peruzzi and Hurt, 2005).***

Under sedation usually produces sudden changes in the level of consciousness because of stress. These changes results in inadequate ventilation, hypertension, tachycardia and discomfort, all of which have adverse consequences for the outcome of ICU patients ***(Fowler et al., 1995).*** Over sedation often occurs as a result of accumulation of sedative and analgesic agents, which can be associated with prolonged mechanical ventilation (MV) and delayed weaning ***(Kollef et al., 1998).***

Aim of the Work

The aim of this study is to compare propofol versus midazolam and the benefit of the sequential use of midazolam and propofol for prolonged sedation of the mechanically ventilated patients in terms of effectiveness of sedation, hemodynamic and metabolic changes and side effects of use of these drugs.

Sedation in ICU

The major goals of analgesia and sedation for critically ill patients in the ICU are to provide control of pain and to facilitate mechanical ventilation, therapeutic and diagnostic interventions. Patients should be easily arousable, calm and co-operative ***(Tonner et al., 2003).***

The Clinicians strive to optimize management by recognizing and treating underlying conditions, using non pharmacologic techniques, selecting the best medication(s) for that individual patient, and administering the lowest effective dose for the shortest possible time. Yet, the medications are imperfect, potentially causing unwanted effects, including idiosyncratic or dose-related side effects, as well as problems related to the immobility and loss of protective reflexes that accompanies deep sedation. Additionally, persistent or excessive drug-induced sedation, particularly accompanying the "cruise control" of continuous infusion, may prolong hospitalization and thus expose the patient to further risks such as added testing, tracheostomy, and ICU complications **(Sessler 2005).**

It is be noted that an algorithm was developed to incorporate many of the assessment issues with the therapy options.When using this algorithm, the pharmacology, potential adverse effects, and therapeutic issues should be considered ***(Jacobi et al., 2002).***

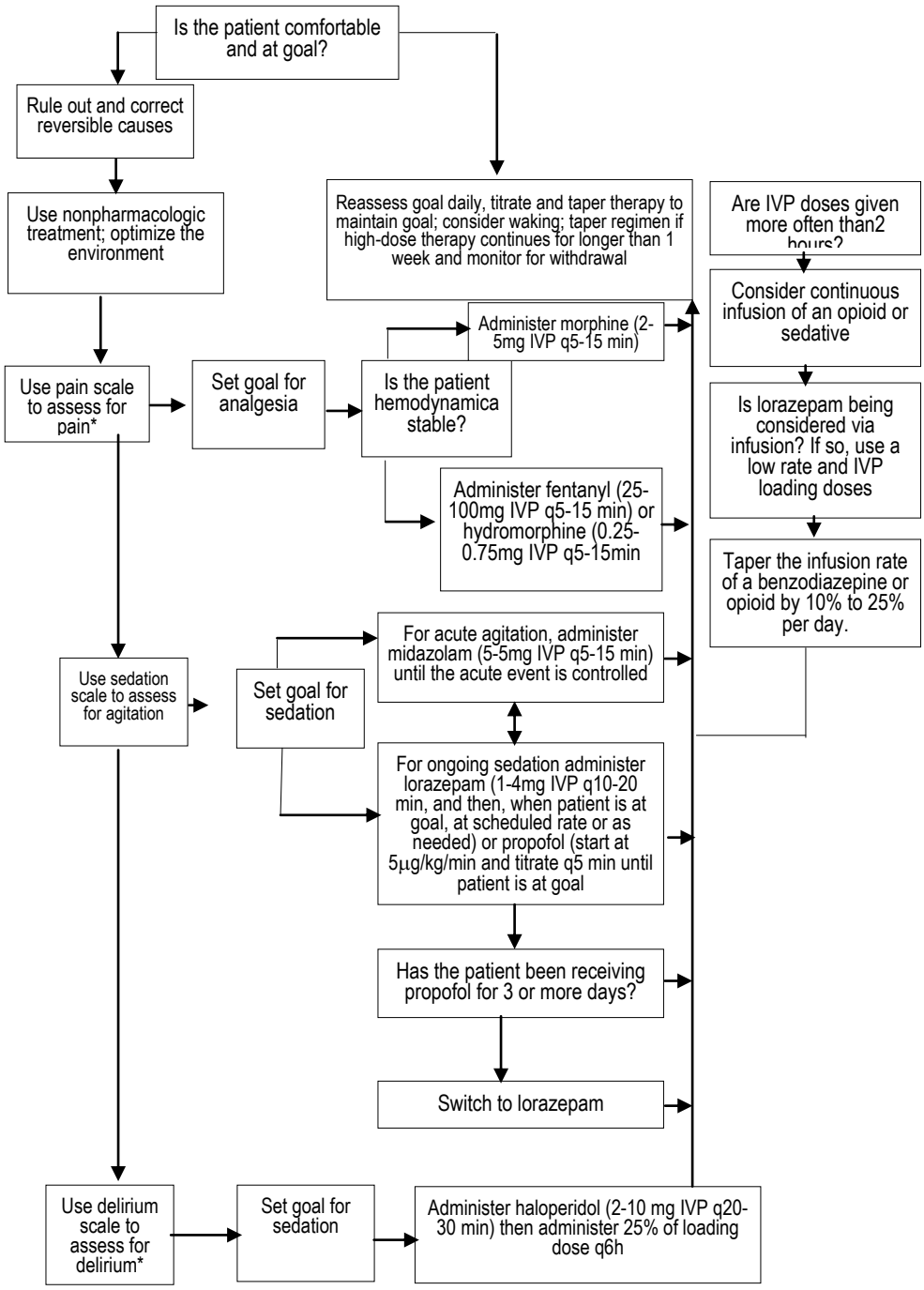

Fig. (1): Algorithm for the sedation of mechanically ventilated patient ***(Jacopi et al., 2002).***

The drugs used for sedation in the ICU are

1. Opioid drugs (morphine, methadone, fentanyl and remifenanyl)
2. Benzodiazepines (midazolam and lorazepam)
3. Propofol
4. Dexmedetomidine (is a centrally acting α_2-agonist with sedative and analgesic properties)
5. Volatile sedation (Isoflurane has successfully been used for sedation in ventilator-dependent ICU patients)
6. Haloperidol which is useful for treating patients with acute agitation and with psychotic behavior but should not be used as a primary agent for sedation
7. Barbiturates**.** ***(Hogarth and Hall, 2004).***

Assessment of sedation in ICU

Many controversies surround the complex issue of patient sedation in the ICU, including how to monitor or quantify sedation ***(Hansen-Flaschen, 1994),*** what level of sedation is appropriate ***(Shapiro, 1994)*** and which medications and protocols are preferred ***(Kress et al., 2002).***The methods that are suitable for assessing the depth of sedation can be considered under two headings (subjective or objective assessment) ***(Hole, 1993).***

Therefore an objective monitor of sedation is crucial for adequately assessing the status of patient particularly in deeply sedated, paralyzed, or drug induced coma patients ***(Tonner et al., 2006)***.

A- Subjective methods (Scoring systems) (Sedation scales):

The use of sedation scales is the most frequently used method of quantifying the sedative effect. More than 25 sedation instruments have been described ***(Turkman et al., 2006).***The Ramsay sedation scale (RSS) was the first to be introduced 30 years ago. Since then, numerous subjective instruments have been developed, validated, and applied in clinical and research settings to monitor level of consciousness or arousal, as well as to evaluate cognition, agitation, patient-ventilator synchrony, and other parameters. These include the Sedation Agitation Scale (**SAS**), the Motor Activity Assessment

Scale.The Vancouver Interactive and Calmness Scale (VICS), the Richmond Agitation-Sedation Scale (RASS), and the Adaptation to Intensive Care Environment (ATICE) instrument ***(DeJonghe et al., 2003)***.

In order for such sedative scale to be effective in the busy ICU setting, the users must be confident that it accurately measures what is intended, that it is reliable, and that it is easy to apply repeatedly by multiple care providers **(Sessler, 2005)**. The ideal assessment scale for sedation would provide measurements simple to compute and record, describe the degree of agitation or sedation accurately within well-defined categories, and guide the titration of drugs to individualized sedation goals, and have validity and reliability in ICU patients ***(DeJonghe et al., 2000).***

Desirable features of a good sedation scale have been enumerated and include the following rigorous multidisciplinary development:

1. Ease of administration, recall, and interpretation
2. Well defined discrete criteria for each level
3. Sufficient sedation levels for effective drug titration
4. Assessment of agitation ***(Sessler et al., 2008).***

Importance of sedation scales is summarized in the following points:

- Avoid over sedation and under sedation.
- Define an optimal end-point for the titration of sedation.

- Provide a semi quantitative score.
- Provide continuity of care and charting.
- Facilitate cost effective use of drugs.
- Allow comparison of drugs.
- Enable precise patient management ***(Ramsay, 2000).***

The subjective assessment of sedation is not optimal because, social, personal and professional factors often influence sedative monitoring and therapy. In addition, with multiple care giver attending to one patient, there is often individual interpretation of the patient's sedative needs ***(LeBlanc et al., 2006)*** i.e. their use is often user dependant as well as they require stimulation of the patient and they are ineffective in patients receiving neuromuscular blocker (NMB) or in deeply sedated patients who are unresponsive to external stimulation ***(Roustan et al., 2005).*** Also physiological parameters can be influenced by Intensive Care Unit (ICU) therapy ***(Turkman et al., 2006).***

In addition, investigators have pointed out that although these scores examine the degree of sedation, they generally do not evaluate whether the patient is coherent or delirious, or in pain. This limits the usefulness of these scores because it is often not possible to know whether the lack of effective sedation is due to delirium or pain ***(Weissman, 2005).***

***The most commonly used sedation scoring s*ystems include:**

1. Ramsay sedation scale.
2. Riker sedation agitation scale.
3. Motor activity assessment scale.
4. Richmond agitation sedation scale.
5. Vancouver interaction and calmness scale.
6. Sedation intensive care score.

1. Ramsay sedation scale (RSS)

It was developed in 1974 by ***Ramsay and co-workers*** for the purpose of monitoring the sedative effect of alphaxolone /alphadolone. In this scale, the level of wakefulness is scored on a scale of 1 to 6 based on a progressive loss of responsiveness to stimuli ranging from auditory to deep painful stimuli (table 1). The utilization of RSS requires very little instruction and therefore is universally used, not only in ICU, but also throughout the hospital ***(Ramsay, 2000).*** Therefore, it continues to be the most widely used scale for monitoring sedation in daily practice, as well as in clinical research ***(Carrasco, 2000).***

Table (1): Ramsay sedation scoring system ***(Ramsay et al., 2000)***

Ramsay score	Clinical parameters for Bedside Assessment of Sedation	Global Degree of Sedation
1	Patient anxious and agitated or restless or both	Varying degrees of awake state
2	Patient cooperative, oriented, and tranquil	
3	Patient responds to commands only	
4	A brisk response to a light glabellar tap, tactile stimuli, or loud auditory stimulus	Varying degrees of asleep state
5	A sluggish response to a light glabellar tap, tactile stimuli, or loud auditory stimulus	
6	No response to a light glabellar tap, tactile stimuli, loud auditory stimulus or nail bed pressure.	

2. The Riker sedation-Agitation Scale (RSAS):

This scoring system was described by ***Riker and co-workers*** for the purpose of controlling treatment with haloperidol in agitated ICU patients.It was developed to assess consciousness and agitation in adult ICU patients, and is composed of one item, with response options ranging from 1 to 7 which describe patient behavior (table 2). RSAS was the first scale proven to be reliable and valid in critically ill adults ***(Riker et al., 1999).***

Table (2): Riker Sedation-Agitation scale ***(Riker et al., 1999)***

Score	Term	Description
7	Dangerous agitation	Pulling at endotracheal tube (ET), trying to remove catheters, climbing over bed rail, striking at staff, thrashing side to side.
6	Very agitated	Does not calm down despite frequent verbal reminding of limits, requires physical restraints, biting ET.
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli of gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands.

3. Motor activity Assessment Scale (MAAS):

MAAS was adapted form the RSAS. It has also been validated and shown reliable for use in critically ill patients. It is a seven point scale to describe patient behaviors in response to external stimuli with response options ranging from 0 to 6 and was developed in surgical ICU patients (table 3), ***(Devlin et al., 1999).***

Table (3): Motor activity assessment scale ***(Devlin et al., 1999)***

Score	Term	Description
6	Dangerously agitated	No external stimulus is required to elicit movement and patient is uncooperative pulling at tubes or catheters or thrashing side to side or striking at staff or trying to climb out of bed and does not calm down when asked.
5	Agitated	No external stimulus is required to elicit movement and patient is attempting to site up or move limbs out of bed and does not consistently follow commands.
4	Restless and cooperative	No external stimulus is required to elicit movement and patient is picking at sheets or tube or uncovering self and follows commands.
3	Calm and Cooperative	No external stimulus is required to elicit movement and patient is adjusting sheet or clothes purposefully and follows commands.
2	Responsive to touch or name	Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs when touched or name is called loudly.
1	Responsive	Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with noxious stimulus
0	Unresponsive	Does not move with noxious stimulus.

4. The Richmond Agitation-Sedation Scale (RASS):

RASS is a 10 point scale in which positive values are used for agitation and negative value are used for sedation. This scale was tested in various types of adult ICUs. The RASS is

extremely simple and follows an innate logic based on the meaning of positive and negative values ***(Peruzzi and Hurt, 2005).***

It has four levels of anxiety or agitation (1 to 4 combative), one level to denote a calm and alert state (0), and 5 levels of sedation (-1) drowsy to (-5) unarousable **(table 4).** RASS has a single-item numerical structure, avoiding the complexity of summing multiple subscale scores ***(Macnab et al., 1991).*** In contrast to some scales, no intervention that requires equipment, such as tracheal suctioning, is done ***(Harris et al., 1991).*** RASS can be administered in 30-60 seconds, using three sequential steps: observation, response to auditory stimulation, and response to physical stimulation. Although two different conditions, sedation and agitation, are evaluated in a single scale, the sequential approach establishes a single score by first assessing agitation and then assessing sedation ***(Sessler et al., 2002).***

An important goal of RASS development was to establish sufficient levels of sedation to permit more precise medication titration. As a target of light to moderate sedation is common for mechanically ventilated patients, RASS was designed to offer multiple levels (0 to -3) within this range. This important range of responses is condensed into one or two sedation levels in other scales. Thus, RASS offers broader

discrimination in the commonly used mild to moderate sedation range ***(Sessler et al., 2002).***

Similar to recently developed scales ***(Devlin et al., 1999),*** RASS contains several levels of agitation. RASS has a logical progression from "restlessness" (+1), which has no immediate impact on patient outcome, to "agitated" (+2), which includes patient-ventilator dessynchrony, to "very agitated" (+3), with immediate risk to patient or staff through tube or catheter removal or aggressive behavior. The highest agitation level is "combative" (+4), which although rare denotes immediate danger for staff from violent patient behavior and has important implications for care of such patients. Documentation of agitated behavior can help guide evaluation for treatable causes of agitation and delirium ***(Ely et al., 2001),*** as well as assess response to therapy ***(Cohen et al., 2002).***

However, there are several potential limitations of RASS. First, it relies on patient auditory visual acuity and is not suitable for patients with severe impairments. Secondly, some patients may be sleeping or sedated but respond to auditory or physical stimulation violently. Although such patients would receive a RASS score on the sedation range, nurses note the excessive response and consider it in their medication titration ***(Sessler et al., 2002).***