Rethinking Sedation and Agitation Management in Critical Illness

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ABSTRACT

Objective: To examine difficulties in sedation management in the critically ill patient and explore how a semi automated sedation controller can improve agitation control. To present recent work on measurements of agitation, dynamic systems modelling and control of patient agitation response.

Data sources: Articles and peer-reviewed studies identified through a PUBMED search and selected original works from the biomedical engineering literature of relevance to agitation control and management.

Summary of review: Over-sedation has an adverse impact on intensive care resources. Interventions to constrain sedation delivery through development of protocols or regular cessation of infusions result in reduction in resource utilisation, but have not significantly addressed existing difficulties in agitation control.

We develop a paradigm in which control of agitation in critically ill patients becomes the primary objective of sedation management. This principle is central to the function of a nurse-managed semi-automated sedation delivery device. The clinical application of this device using subjective assessments of agitation is presented. A framework for the development of improved automated sedation delivery systems using objective measurements of agitation and control, based on agitation feedback, is described. Using dynamic systems modelling and a simulated nurse, a bolus-driven approach significantly reduced agitation and minimised drug utilisation. This result challenges the current practice of sedating patients using continuous infusions.

Conclusions: A simple computerised interface with an algorithm that continually reduces the infusion rate in the absence of agitation has successfully been introduced into clinical practice. Nursing staff reported high levels of satisfaction with this device and it has enabled detailed data on patterns of sedation administration to be extracted for analysis. This data has been used to validate a model of the fundamental agitation-sedation dynamics. (Critical Care and Resuscitation 2003; 5: 198-206)

Key words: Sedation, patient agitation, monitoring, sedation protocol, sedation management, feedback control, automated

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Provision of sedation and analgesia in critically ill patients is one of the most arbitrarily applied treatments in medicine, with considerable differences in practice throughout the world. Over-sedation is usually the result of interventions to control agitation and delirium, causing an increase in number of interventions, length of mechanical ventilation and intensive care stay.\(^1\) Constraining sedation through use of sedation-agitation scales, or stopping drug infusions each morning have been moderately successful,\(^2,3\) but in spite of these results, many intensive care units do not use sedation protocols, relying instead upon the judgement and experience of intensive care unit staff.

Unfortunately, none of these approaches addresses the problem of agitation control. Agitation manifests as excessive motor or verbal activity, accompanied by activation of the sympathetic nervous system. It interferes with therapeutic procedures and compromises safety of the patient and medical staff. Patients frequently cycle from high levels of agitation to prolonged periods of over-sedation.\(^4\) It is important to know whether the agitation-sedation cycling results from the patient’s condition or because of our attempts to control agitation. If poor agitation control is due to ‘therapeutic failure’ then it is essential to gain a better understanding of this phenomenon.

Understanding the process of agitation control

The intensive care nurse uses intuition and experience to gauge a patient’s agitation or sedation level based predominantly on movement and changes in heart rate, blood pressure, respiratory rate. Together with other subjective assessments this information is integrated to produce what is effectively a personalised agitation score. The nurse uses this data to provide additional sedation to produce their desired outcome, all of which can vary from nurse to nurse. The process is repeated as necessary to control agitation. However, this entire subjective approach is imprecise, lacks consistency and often leads to cycling between agitated and over-sedated states.

Published scoring systems provide a measure of consistency, but place agitation and sedation at either end of a linear scale.\(^4,5\) However, agitated critically ill patients nearly always have a reduced level of consciousness that is indistinguishable from the effects of sedation. Thus, it is impossible to select a single point on a linear scale that defines a patient’s agitation-sedation state. We split the Riker sedation-agitation scale\(^4\) into separate sedation and agitation scales, creating separate measures of each as a patient can often be both sedated and agitated (Table 1).

<table>
<thead>
<tr>
<th>Sedation Scale</th>
<th>Agitation Scale</th>
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<tbody>
<tr>
<td>-3 Unresponsive</td>
<td>+3 Dangerous agitation</td>
</tr>
<tr>
<td>-2 Responsive to tracheal suction or pain</td>
<td>+2 Moderately agitated</td>
</tr>
<tr>
<td>-1 Responds to voice</td>
<td>+1 Mildly agitated</td>
</tr>
<tr>
<td>0 Calm and cooperative (or sleeping)</td>
<td>-1 to -3 Agitated</td>
</tr>
</tbody>
</table>

A semi-automated sedation delivery system

Our intention was to use an agitation level, not sedation level, as the primary endpoint in sedation management. In the vast majority of cases, nursing staff readily titrated sedation to an acceptable and safe level of agitation. Where mild agitation may not have been tolerated (e.g. in severe head trauma), thresholds for treating agitation were reduced and an increased level of sedation was tolerated.

We developed an algorithm that reduced the background infusion of morphine (1.0 mg/mL) and midazolam (0.5 mg/mL) as a proportion of the total amount of drug used to manage agitation over the preceding 4 hours.\(^6\) Hence, only a proportion of the background sedation was carried through to the next time period, reducing the rate of infusion in the absence of agitation. As long as agitation was present, a background infusion continued. If the patient became less agitated, less sedation was given and the background infusion rate was reduced accordingly.

In most cases, sedation could be regarded as a useful side effect of treating agitation. However, from time to time it is necessary to induce sedation or analgesia in order to carry out uncomfortable or painful procedures. Here the intent is clearly different from the intent to reduce agitation given the different clinical endpoints. Therefore, this additional sedation was recorded separately and not used to determine the background infusion rate. For these reasons it is not surprising that devices marketed for sedation monitoring in the operating room have added little to sedation management in intensive care.\(^7\)

The algorithm was successfully trialed using a paper flow chart (Figure 1). A modification of this algorithm allowing hourly adjustments of the background infusion has since been incorporated into a simple user interface connected to the serial port of the Graseby 3500 syringe pump\(^8\) (Infuse-Rite\(^©\), Figure 2). Nursing staff select ‘infusion bolus’ when increasing sedation to lessen agitation, or ‘procedural bolus’ to increase the sedation level.
**Figure 1. Sedation algorithm chart.**

**Figure 2. Infuse-Rite™ controller attached to Graseby 3500 syringe pump.**
The Infuse-Rite also records all drug delivery data, which is available for the patient record, audit and research. Our approach has been successful, with nursing staff reporting high levels of satisfaction with regard to agitation-sedation control, patient and personal safety and time efficiency. Data taken from a survey of 30 nurses from the Christchurch Hospital Intensive Care Unit who had more than 1 year’s experience and who were asked to compare the new system with previous approaches are shown in Figure 3.

The rules are easily understood and the background infusion is continuously reduced in the absence of agitation, minimising over sedation. When agitation levels are used as clinical endpoints the need for combined sedation-agitation scales is obviated.

The Infuse-Rite provides a simple user interface allowing titration of sedation to agitation level. Its success relates to consistency in terms of simple input rules and algorithmically determined outputs. However, this semi-automated controller still has limitations. In particular, input in the form of agitation assessment is subjective and prone to error while its output uses fixed parameters that may not suit every patient. In addition, this approach is still infusion focused in spite of the fact agitation response is highly variable.

To effectively control agitation with a continuous infusion necessitates that sedation be given in excess of requirements, unless monitored and modified frequently. The Infuse-Rite compensates for this shortcoming by automatically reducing the background rate in the absence of agitation. An ideal sedation controller would immediately respond to changes in agitation by giving timely and appropriate boluses of sedation, a true feedback control system.

Objective measurements of agitation, an ‘agitation sensor’, is the first step towards a truly automated means of agitation control. The second step is linking this objective measurement into a dynamic model of the fundamental agitation-sedation dynamics. Preliminary work on quantifying agitation and using this information in a dynamic systems model as a feedback variable to optimise sedation and minimise agitation is presented.

Objective measurement of agitation

Heart rate variability (HRV) and blood pressure variability (BPV) are commonly used for analysing sympathetic and parasympathetic nervous system interactions, and may be indicators of agitation and stress.

The physiological responses to induced agitation in 12 normal subjects were studied. Mental stress and physical pain were induced using a Stroop Colour Word Conflict Test (CWT) and a cold pressor test (CP). Between tests, subjects were allowed to rest and return.
to a ‘calm state’ before another test was carried out. These data were used to develop an objective agitation metric. Intensive care patients were then monitored and an agitation score correlated to nursing assessed agitation using the modified Riker sedation-agitation scale detailed in Table 1. Approval from the Canterbury Ethics Committee was obtained for this study.

There were four basic signal processing steps employed in quantifying agitation based on HRV and BPV.\textsuperscript{11,12}

The method has been previously presented,\textsuperscript{11,12} and is designed to minimise the impact of noise and variable signals. The method avoided the difficulty associated with using long windows of data and enabled transient changes in the HRV and BPV signals to be captured on a sample to sample basis in real-time, using adaptive signal processing techniques. The variability ratios of very low frequencies (VLF)/high frequencies (HF) for HRV were observed to rise during periods of agitation as heart rate rose and variability declined. Similarly, HF/VLF for the BPV signal increased when systolic blood pressure rose and variability increased. These results were found in both normal and critical care subjects. An overall agitation score is obtained from this data using a series of rules based on medical experience and observation that are encapsulated in a fuzzy logic neural network. The result is a patient agitation level on a scale in the range from zero to 1 for each metric. A similar process is applied directly to systolic blood pressure values to create a third metric.

For each physiological signal, three values are used to determine the agitation score, the signal itself and its mean over the prior 10 and 30 minutes. This approach enables transient changes in the signal to be tracked. The resulting agitation levels for each signal may then be further combined or examined separately. Figure 4 shows the resulting patient agitation level calculated from the patient’s HRV (solid) and BPV (dashed) signals. The x-axis shows the time in minutes as well as the agitation level as evaluated by nurses using the modified Riker sedation-agitation scale. The approach shows good correlation with subjective agitation scores by nursing staff for both agitated and calm periods.

Implementation of this physiologically based agitation quantification method in a real-time environment is readily achievable due to its relatively low computational intensity. In particular, the adaptive signal processing methods employed enable fast processing and readily handle the typically non-stationary physiological signals encountered.

Movement also plays a significant role in the various subjective scales used to measure agitation, such as the Riker sedation-agitation scale or the Motor Activity Assessment Scale (MAAS).\textsuperscript{13} Many nurses use the patient’s motor activity to assess the adequacy of sedation,\textsuperscript{14,15} with different motor activity classified by the different types of movement and the muscles involved. Movement of large muscle groups is an indicator of agitation, whereas movement of limb, neck and facial muscles is acceptable. In contrast, constant lack of small muscle movement equates to oversedation.\textsuperscript{15}

Using digital imaging to measure patient motion enables another form of quantified measurement for determining patient agitation. Similar to the processing of HRV and BPV, motion is measured and fuzzy logic rules used to generate a final agitation level in the range zero to 1. In this case, the issue is to separate out motion

Figure 4. Typical intensive care patient data with nurse evaluated agitation on x-axis and agitation level scaled (0-1), calculated from systolic blood pressure variability (BPV) and heart rate variability (HRV) on the y-axis.
associated with agitation from those of nurses performing various tasks.\textsuperscript{16,17}

A simple block correlation method examines each frame and assesses the differences between successive, or groups of successive, frames, and is used to quantify the amount of motion. These differences can be summed over a region, or the entire frame, and a power value determined which is proportional to the amount of movement. In this research, each frame is broken into different regions of interest (ROI’s), as shown in Figure 5, to enable patient motions to be precisely defined and nursing motions to be eliminated. The edge regions in Figure 5 are used to detect nursing motions. When nurses are in the frame, their motion can be correlated to that of the patient and thus how much the measured patient movement was influenced by nurse movement.

Typical results for three different intensive care patients, along with the nursing assessed Riker sedation-agitation scale, are shown in Figure 6 for different levels of agitation.

![Figure 5. Assessment of movement with frame regions of interest (ROI) shown.](image)

**Modelling Agitation**

A model of the essential dynamics of the agitation-sedation system has recently been proposed for use in developing automated sedation infusion protocols.\textsuperscript{3}

\[
\begin{align*}
\dot{C}_c &= -K_1 C_c + \frac{U}{V_d} \\
\dot{C}_p &= -K_2 C_p + K_4 C_c \\
\dot{A} &= S - \int_0^t C_p(\tau) e^{-K_1 (t-\tau)} d\tau
\end{align*}
\]

Where $C_c$ and $C_p$ are drug concentrations in the central and peripheral compartments, $U$ is the intravenous infusion rate, $S$ is the stimulus invoking agitation and $A$ is an agitation index and $K_4 - K_1$ are drug elimination rate constants.

Conceptually, input from objective agitation measurements is used to drive a syringe pump to minimise agitation. In the current absence of objective agitation measurements, downloaded data from the Infuse-Rite controller have provided a surrogate of agitation response to test this model. This assumption is valid because the Infuse-Rite controller requires nursing staff to indicate their intent to either reduce agitation, or induce sedation by activating the ‘infusion’ or ‘procedural’ bolus button respectively. Therefore, the pattern of infusion boluses mirrors agitation in a particular patient.

This model was verified using data from 37 intensive care patients, modelling the nursing input as a derivative feedback controller using constant patient-specific parameters, and the Infuse-Rite controller filter.\textsuperscript{18} Good correlation between the model and actual infusion data was found for these simulations as seen in Table 2. The average tracking index across all patients was 82.7, with a range varying between 71.9 and 93.0. The tracking index is a measure of how well the simulated infusion profile matches the actual profile, which is attempting to replicate in this simulation, with a perfect match scoring 100. The relative total dose varies between 77% and 95% with an average of 88.6%. The minimum time period simulated for a given patient is 48 hours with several patients having data recorded for more than 200 hours.

Table 2 also presents the results obtained for both the relative dose and agitation level when the control gains used for the simulated nurse are increased and the Infuse-Rite controller used in clinical practice is removed. Removing the Infuse-Rite filter enables a more responsive control without the need to filter out the effects of error from subjective assessment of patient agitation. Hence, these simulations examine the potential for improved automated systems given an objective feedback measurement of agitation.
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Figure 6. Patient agitation level for three ICU patients. Peaks correspond to subjective assessments by nursing staff.

Table 2. Summary of simulation results for 37 patients

<table>
<thead>
<tr>
<th></th>
<th>Tracking Index</th>
<th>Relative total dose (%)</th>
<th>Relative agitation performance indicators (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Simulated Nurse</td>
<td>Simulated Nurse</td>
<td>Gains x2</td>
</tr>
<tr>
<td>Maximum</td>
<td>93.0</td>
<td>95.0</td>
<td>116.4</td>
</tr>
<tr>
<td>Average</td>
<td>82.7</td>
<td>88.6</td>
<td>89.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>71.9</td>
<td>77.0</td>
<td>64.1</td>
</tr>
<tr>
<td>SD</td>
<td>5.1</td>
<td>3.4</td>
<td>10.4</td>
</tr>
</tbody>
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Reductions in agitation are observed as the unfiltered gains are uniformly increased. The peak agitation level was reduced on average 37.8% to 62.2% of levels seen in the simulated nurse by increasing the gains by a factor of two. Mean patient agitation levels are reduced on average 44.2% to 55.8% of the simulated nurse levels. Further reductions are observed when the gains are uniformly increased by a factor of three. Observed infusion profiles become more exaggerated and the peak infusion rate increases as the gains are increased. While the peaks are considerably higher, the infusion rate also drops dramatically in the absence of agitation, representing a bolus-focused approach to sedation administration. This result is shown in Figure 7 for a typical patient, where the solid lines are for doubled control gains, the dotted lines are for tripled control gains, and the grey filled area is the original infusion profile for comparison. Note that for tripled gains the average relative total dose decreases, so a better performance is obtained using less sedative. The average relative doses for doubled gains are similar to the original infusion, providing improved agitation control for the same dose used by the Infuse-Rite system.
Our approach uses simple rules based on agitation levels to guide sedation delivery. A simple computerised interface with an algorithm that continually reduces the infusion rate in the absence of agitation has successfully been introduced into clinical practice. This method essentially provides a bolus-driven approach with the potential to produce significant reductions in agitation while minimising drug consumption, and challenges the conventional wisdom of using continuous sedative infusions. Nursing staff reported high levels of satisfaction with this device and it has enabled detailed data on patterns of sedation administration to be extracted for analysis. This data has been used to validate a model of the fundamental agitation-sedation dynamics.

A consistent approach to managing sedation using computerised protocols with objective agitation measurement could simplify sedation administration and minimise drug consumption. Intensive care access and quality could also be improved significantly through reductions in length of stay, staff workload and cost.

REFERENCES

Figure 7. Typical effects of increasing control gains on infusion (U) and agitation (A).


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