Utilization Pattern and Cost of Sedation, Analgesia and Neuromuscular Blockade in a Multidisciplinary Intensive Care Unit

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ABSTRACT

Objectives: *To study the utilization pattern and the cost of sedatives, analgesics and neuromuscular blocking agents in a multidisciplinary intensive care unit (ICU)*

Methods: *A prospective observational study was conducted in the ICU of the Eric Williams Medical Sciences Complex, Trinidad and Tobago, for a period of twelve weeks. All patients admitted to the ICU were enrolled. No interventions were done. Data collected included demographics, diagnoses on admission, length of stay in the ICU, status of mechanical ventilation, patient outcome, quantity of sedatives, analgesics and neuromuscular blocking agents used in every patient and their cost.*

Results: *There were 333 patient-days encountered from 34 patients studied. Midazolam, fentanyl and cisatracurium were the most commonly used sedative, opioid and neuromuscular blocking agents respectively. The total cost of drugs used for sedation, analgesia and neuromuscular blockade was approximately US$ 19 600 per annum. Cost for this treatment alone accounted for more than 50% of the total ICU drug costs. The costs were significantly higher in patients who stayed more than two weeks in the ICU when compared to those who stayed less than two weeks (*$p < 0.001$*).*

Conclusions: *The study highlights the utilization pattern and financial burden of sedation, analgesia and neuromuscular blockade in the delivery of critical care.*

Patrón de Utilización y Costo de la Sedación, Analgesia y Bloqueo Neuromuscular en una Unidad Multidisciplinaria de Cuidados Intensivos

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RESUMEN

Objetivos: *Estudiar el patrón de utilización y costo de los sedantes, analgésicos, y agentes de bloqueo neuromuscular en una Unidad Multidisciplinaria de Cuidados Intensivos (UCI).*

Métodos: *Se llevó a cabo un estudio prospectivo en la UCI del Complejo de Ciencias Médicas Eric Williams, en Trinidad y Tobago, por un período de doce semanas. Todos los pacientes ingresados a la UCI fueron enrolados. No se realizaron intervenciones. Los datos recogidos incluyeron demografías, diagnósticos de ingreso, longitud de la estadía en la UCI, estatus de ventilación mecánica, evolución del paciente, así como la cantidad y el costo de los sedantes, analgésicos y agentes de bloqueo neuromuscular usados en cada paciente.*

Resultados: *Se encontraron 333 días-pacientes a partir de 34 pacientes estudiados. La midazolama, el fentanil y el cisatracurio fueron los agentes sedativos, opioides y de bloqueo neuromuscular más comúnmente usados. El costo total de los medicamentos usados para la sedación, la analgesia y el bloqueo neuromuscular fue de aproximadamente $19 600 USD por año. El costo sólo para este tratamiento representó más del 50% del total de los costos de medicamentos de la UCI. Los costos fueron significativamente más altos en pacientes que permanecieron más de dos semanas en la UCI, en comparación con aquellos que permanecieron menos de dos semanas (*$p < 0.001$*).*

Conclusiones: *El estudio pone de relieve el patrón de utilización de la carga financiera de la sedación, analgesia y bloqueo muscular a la hora de ofrecer atención crítica.*

West Indian Med J 2008; 57 (2): 112

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INTRODUCTION

Sedation, analgesia and neuromuscular blockade are commonly used in patients admitted to intensive care units (ICUs) (1, 2). These consume a larger part of the budgetary allocations of the drugs used in the ICU (3). More efficient utilization of these drugs is vitally important not only to cut ICU costs but also to prevent morbidity in patients (4, 5). In some circumstances, neuromuscular blocking agents are used, with no pharmacological therapeutic value, to facilitate ease of handling patients. Due to the widespread misuse of these agents, guidelines have been published to regulate their use in ICU. In 1995, the Society of Critical Care Medicine (SCCM) of the United States of America (USA) established guidelines for the use of neuromuscular blocking agents in ICUs and these were revised and updated in 2002 (6, 7).

The use of neuromuscular blocking agents for a prolonged period of time is associated with many potential complications in ICU patients (8). Hence, the indications for neuromuscular blockade must be defined clearly, patients should be constantly evaluated during the treatment for the need of continued muscle relaxation and the smallest doses of neuromuscular blockade that will accomplish clinical goals should be used (9).

Long-term use of neuromuscular blocking agents is associated with myopathy in critically ill patients (10). This has lead to questions regarding the role of these agents in the ICU (11). In addition, other disadvantages such as prolongation of mechanical ventilation and difficulty weaning from mechanical ventilatory support have been attributed to their use (12–14). Hence sedation and neuromuscular blockade should also be appropriately monitored (15).

With this background, we conducted a study to determine the usage of sedatives, analgesics and neuromuscular blocking agents in the ICU of the Eric Williams Medical Sciences Complex, a University teaching hospital in Trinidad and Tobago, West Indies. To our knowledge, very little information regarding the utilization pattern and pharmaco-economic impact of sedation and neuromuscular blockade in ICU has been published from the Caribbean.

SUBJECTS AND METHODS

This prospective, observational study was conducted on a daily basis during the period November 2005 through January 2006 in the multidisciplinary ICU in the Eric Williams Medical Sciences Complex, Trinidad and Tobago, West Indies.

Approval was obtained from the Ethics Committee of the Faculty of Medical Sciences, The University of the West Indies, St Augustine, and from the hospital authorities. Collection of data was observational and no new interventions were done for the purpose of the study *per se*.

The multidisciplinary ICU in the Eric Williams Medical Sciences Complex is a six bed open unit admitting both adult and paediatric patients belonging to all medical and surgical specialties. Patients get admitted from the Priority Care Facility (Emergency Department) directly, from the operating rooms and general wards.

All patients admitted to the ICU during the three-month period were enrolled in the study. Patients who were staying for a long-term (more than 6 months) and patients who stayed less than a day in the ICU (predominantly for high-dependency care) were excluded from the study.

The following data were collected: patient's demographics (including patient's age, weight and gender), diagnosis on admission, status and duration of mechanical ventilation, length of stay in ICU, administered doses of sedatives, analgesics and neuromuscular blocking drugs, other drugs (*eg* aminoglycosides and magnesium sulphate) and the cost of drugs.

The amounts of sedative, analgesic and neuromuscular blocking drugs were recorded in each patient and data were collected from the 24-hour nurse's flow-chart. The total amount of drugs per patient per day, administered both *via* intravenous infusions and intravenous boluses were recorded. The cost of the drugs was obtained from pharmacy department and the total cost per day was calculated as the product of the unit usage of a drug and the cost of each unit utilizing a 'bottom-up' method.

For the purpose of analysis, patients were divided into two groups: those who stayed less than two weeks and those who stayed more than two weeks in the ICU. Conventionally, patients who stayed more than 14 days in ICU were considered to be long-stay patients (16).

Descriptive analyses of the data were done. Data having non-Gaussian distribution are reported as median and interquartile ranges (IQR) and analysed using Wilcoxon ranked sum test. Categorical data were analysed by Chi-squared test. Other continuous data were reported as mean and standard error of mean (SEM). Statistical significance was fixed at the level of $p < 0.05$. Data analysis was done using the software Statistical Package for Social Sciences (SPSS™) (Chicago, IL, USA) version-12.0.

RESULTS

During the three-month study period, 46 patients were admitted to the ICU. There was one long-term ICU patient who stayed in the ICU for three years. This patient was not included. There were 12 patients (26% 95% CI 13, 39) who stayed less than one day in the ICU for high dependency care and were excluded. These patients were not receiving mechanical ventilatory support and did not require sedation and analgesia. Thirty-four patients were included for data collection. There was an equal distribution of gender. Among female patients, 6 (35%) were adults and 11 (65%) were children; among male patients, 9 (53%) were adults and 8 (47%) were children. Overall, 333 patient-days were encountered during the study period.

The age of patients ranged from one day to 73 years, the median age being 19 years [1.75, 48.5 (IQR)]. All patients received mechanical ventilation. Admitting diagnoses of patients were further categorized according to the various organ systems affected and is shown in Table 1.

Table 1: Diagnostic categories

Organ Systems	Number of patients (%)
Respiratory system	8 (23.5)
Central Nervous nervous system	7 (20.6)
Cardiovascular system	7 (20.6)
Gastrointestinal system	6 (17.6)
Multi-organ dysfunction	5 (14.7)
Other	1 (3)

The patients were categorized, according to the duration of ICU stay, into two groups namely those who stayed less than two weeks and those more than two weeks. Chi-squared analysis was done to determine the difference in the outcome between these groups; however this was not statistically significant (Chi-square value = 0.08, df: 1, p = 0.78).

The majority of the patients received midazolam, cisatracurium and fentanyl as boluses and infusions. Combinations of drugs were commonly used. The most commonly used sedative was midazolam which was usually administered as infusions. Other sedatives included propofol which was also administered as infusion. The commonly used opioids were fentanyl, morphine, pethidine and tramadol, administered as boluses as well as infusions. Fentanyl was used in most patients before endotracheal suctioning to attenuate the haemodynamic response. The proportion of patients receiving the various sedatives, analgesics and neuromuscular blocking agents is depicted in Fig. 1.

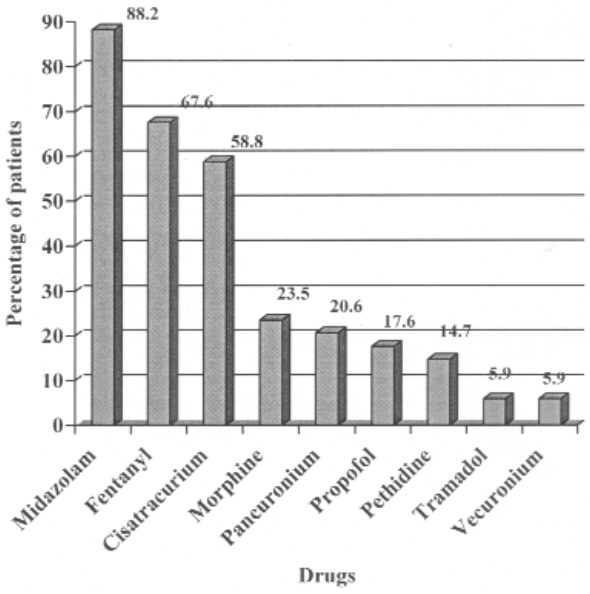

Fig. 1: The frequency of usage of sedatives, analgesics and neuromuscular blocking agents

Cisatracurium, pancuronium and vecuronium were the neuromuscular blocking agents used, of which, cisatracurium was the most commonly used and vecuronium was the least commonly used agent. Aminoglycosides and magnesium sulphate were used in six patients.

Tables 2 and 3 depict the usage of the drugs and their costs respectively. The usage and costs of midazolam, fentanyl and cisatracurium, are expressed in median values and IQR, while those for propofol, morphine, pethidine, tramadol, pancuronium and vecuronium are given as mean values and standard error of mean (SEM).

Table 2: The usage of sedative analgesics and neuromuscular blocking agents

Drug	Usage (mg)		
	Median (IQR)	**Maximum***	**Total†**
Midazolam (n = 30)	74 (7.5, 461.5)	1350.50	9207.05
Fentanyl (n = 23) (μg)	50 (0, 385)	2150.00	9152.00
Cisatracurium (n = 20)	6.5 (0, 118.25)	801.90	3566.17
	Mean (SEM)	**Maximum***	**Total†**
Morphine (n = 8)	53.9 (25.8)	608.62	1781.42
Pancuronium (n = 7)	13 (9.1)	300.00	429.85
Propofol (n = 6)	8.1 (4.7)	120.00	267.80
Pethidine (n = 5)	56.9 (33.4)	875.00	1765.00
Tramadol (n = 2)	43.3 (32.4)	959.00	1384.00
Vecuronium (n = 2)	1.6 (1.3)	40.30	53.93

* Maximum dose a single patient received (Minimum dose = 0)
† Total amount of drug used during the study period
IQR = Interquartile ranges
SEM = Standard error of mean

Table 3: The cost of sedatives, analgesics and neuromuscular blocking agents

Drug	Cost (TT $)		
	Median (IQR)	**Maximum***	**Total†**
Midazolam (n = 30)	51.8 (5.25, 323.05)	945.35	6444.94
Fentanyl (n = 23)	37.09 (0, 674.73)	67.72	288.29
Cisatracurium (n = 20)	1.58 (0, 12.13)	4575.64	20348.57
	Mean (SEM)	**Maximum***	**Total†**
Morphine (n = 8)	14.7 (7.0)	165.97	485.79
Pancuronium (n = 7)	80.4 (56.4)	1852.50	2654.32
Propofol (n = 6)	1.5 (0.84)	21.45	47.87
Pethidine (n = 5)	3.2 (1.9)	49.88	100.61
Tramadol (n = 2)	3.5 (2.6)	76.72	110.72
Vecuronium (n = 2)	18.8 (14.7)	464.20	620.73

* Maximum expenditure in one single patient (Minimum cost = 0)
† Total expenditure during the study period
IQR = Interquartile ranges
SEM = Standard error of mean
1 US $ = 6.3 Trinidad and Tobago dollar (TT $)

There was no evidence of the use of any sedation scale and peripheral nerve stimulator for monitoring sedation and neuromuscular blockade in the ICU during the study period.

A Wilcoxon ranked sum analysis was done to determine the difference between patients who stayed less than and more than two weeks in the ICU with respect to the usage and costs of midazolam, fentanyl and cisatracurium. This showed a statistically significant difference ($p < 0.001$) and is shown in Table 4. However, the same analysis between survivors and non-survivors did not show any statistical significance.

Table 4: Comparison between short and long stay patients

Variable	# 14 days stay (n = 27)	> 14 days stay (n = 7)
Age (Median, IQR)	16 (2, 48)	22 (0.75, 50)
Hospital mortality (%)	37	42.9
Midazolam usage (mg) (Median, IQR)	33.7 (4.5, 126.8)	1005 (824, 1322)*
Midazolam cost (TT$) (Median, IQR)	23.5 (3.2, 88.7)	703.7 (576.8, 925.4)*
Cisatracurium usage (mg) (Median, IQR)	4 (0, 21.3)	251.3 (24, 584)*
Cisatracurium cost (TT$) (Median, IQR)	22.8 (0, 121.5)	1433.9 (136.9, 3332.3)*
Fentanyl usage (μg) (Mean, SEM)	99 (30.3)	938 (266)*
Fentanyl cost (TT$) (Mean, SEM)	3.1 (0.9)	29.5 (8.4)*
Total cost of treatment (TT$) (Median, IQR)	121.2 (19.2, 356)	1665.5 (758, 4134.2)*

* $p < 0.001$ by Wilcoxon ranked sum test
1 US $ = 6.3 Trinidad & Tobago dollar (TT $)

The median costs of sedation, analgesia and neuromuscular blockade was US$29.44 (5.17, 196.18 IQR) for the duration of study. The total expenditure in the ICU during the study period which is attributable to sedation, analgesia and neuromuscular blockade was US$4936.80. During the study period, the maximum cost in a single patient for these medications was US$670.30. The cost for these drugs according to diagnoses is shown in Fig. 2; the costs were relatively higher for trauma patients.

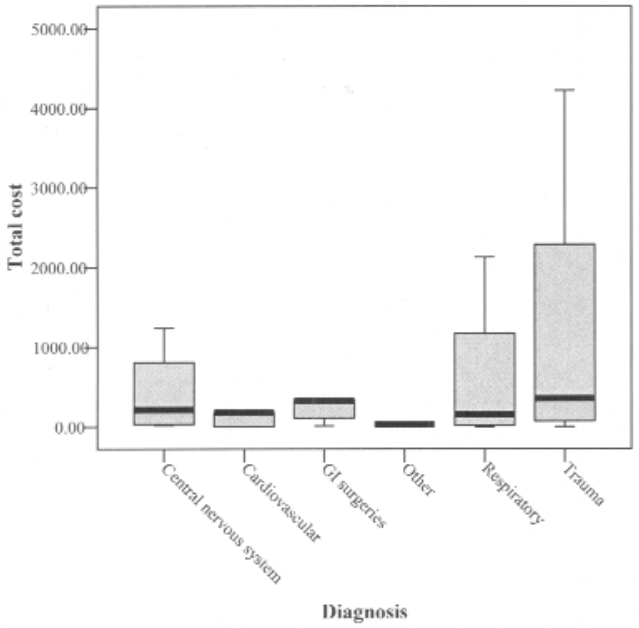

Fig. 2: Costs of drugs used for sedation, analgesia and neuromuscular blockade according to diagnostic categories (TT $)

1 US $ = 6.3 Trinidad & and Tobago dollar (TT $)

DISCUSSION

Sedation, analgesia and neuromuscular blockade practices in the ICU widely vary in different parts of the world (17–22). Most of the published reports are from the developed world. Intensive Care Unit practices and performance in many developing countries are currently comparable to those in the developed world, although the available resources are always a major constraint (23).

In the study ICU, midazolam was the only benzodiazepine used for sedation. Midazolam has been the preferred drug of choice as reported in many other studies probably because it is relatively inexpensive and it has established safety profiles (24, 25). Although lorazepam has been shown to be cost-beneficial, it has been predominantly used in adult ICUs (26, 27). Until recently, the study ICU was a paediatric ICU and lorazepam was not the conventional choice for sedation. Due to the high usage pattern and the attendant high cost of midazolam in the present study, it may be recommended that lorazepam could be used for adult patients. The cost benefits of implementing this change will have to be investigated.

Propofol is another common sedative in many ICUs although some studies have reported the preference for midazolam over propofol (25). In the study ICU, propofol was not commonly used probably because of the cost factor and the prolonged requirement of sedatives in most of the patients. A previous study found that pharmacist interventions in the ICU reduced the cost impact of propofol but also improved patient outcomes (28). In our situation, due to staff shortages, there has been no input from a clinical pharmacist regarding the drug usage in ICU.

Morphine is the most preferred opioid analgesic in an ICU setting (5). In the study ICU, fentanyl was much more commonly used than other opioids. This may be due to the fact that fentanyl was administered prior to suctioning procedures rather than as a strict analgesic. Fentanyl has been known to attenuate the haemodynamic response to intubation and instrumentation of the trachea which is a very common occurrence in the ICU during frequent endotracheal suctioning. The total cost of fentanyl is justified in this respect. Also, it must be noted that despite its frequent use, the cost of fentanyl was significantly less than that of morphine.

Other opioids used in the study ICU include pethidine and tramadol. These drugs are not routinely used in the ICU setting. Pethidine is not usually advised due to the neurotoxic effects of its metabolite norpethidine in the ICU environment (29). Tramadol has not been well studied in children, it has an increased incidence of nausea and vomiting and the cost is approximately twice that of fentanyl. However, the relatively lesser respiratory depression associated with tramadol when compared to morphine and pethidine would have been the reason for its use as an analgesic in some adult patients in the ICU.

We found that there was a widespread use of the neuromuscular blocking agents in the ICU. Cisatracurium was the most widely used neuromuscular blocking agent, predominantly as infusions and the total cost was over US$3200. Only when cisatracurium was unavailable, vecuronium and pancuronium were used when cisatracurium was unavailable. It is noteworthy that the unit cost of the latter two drugs exceeds that of cisatracurium. Despite paediatric admissions, there has been a high utilization of the neuromuscular blocking agents in the study ICU, perhaps due to the convention of the institution. Neuromuscular blocking agents are often used to prevent accidental self-extubation by children and physical restraints are not used in children in the study ICU. A previous study has reported self-extubation and the use of physical restraints in the ICU and its corroboration with sedation and neuromuscular blockade (30).

Aminoglycosides and magnesium sulphate were used in some patients although there were no adjustments made in the dosage of neuromuscular blocking agents for these patients. These drugs are known to prolong the effect of neuromuscular blocking agents and thus may contribute to the increased length of stay of patients in the ICU (31).

The other major findings of the present study include a lack of a formal protocol for administering neuromuscular blocking agents, sedatives and analgesics, non-existence of an established sedation scale to directly assess the level of sedation in the patient and the lack of a peripheral nerve stimulator to monitor the effect of neuromuscular blocking agents. Patients receiving neuromuscular blocking agents should be assessed both clinically and by train-of-four monitoring by a peripheral nerve stimulator with the goal of adjusting the degree of neuromuscular blockade to achieve one or two twitches (32). This can minimize the possibility of over-dosage or under-dosage, and assist in the evaluation of recovery.

A sedation scoring system should ideally be implemented to monitor and subsequently reduce costs. The Ramsay Scale, when effectively implemented, is said to reduce the duration of mechanical ventilation and the ICU length of stay, although some authors have questioned the ability and have stressed the need for better methods (33). The Brussels sedation scale claimed to reduce excessive sedation in mechanically ventilated patients, but there was no mention of the overall outcome (34). Notwithstanding these claims, use of sedation scales has been reported to be low in many countries, for example, 18% in Austria and 16% in Danish ICUs (20, 21). Hence it is not totally surprising that no such scale is in use in our situation.

Institution of a protocol regulating the use of sedatives, analgesics and neuromuscular blocking agents has been shown to be beneficial in the ICU and may minimize costs (30). Another study showed the reduction of the usage of neuromuscular blocking agents from 30% to 5% following implementation of guidelines (13). Absence of such guidelines in the study ICU could have contributed to the increased use of neuromuscular blocking agents.

Our previous research in the same ICU setting has shown that the total cost of drugs used per annum was US$34 346 (35). If the costs from the present study are extrapolated to expenditure per annum, the ICU spends approximately US$19 600 on sedation, analgesia and neuromuscular blockade alone. Then it follows that 57.5% of the drug costs in ICU is attributable to sedation, analgesia and neuromuscular blockade. Critical care pharmacists' input in this area may be valuable to determine the trend of usage and also in formulating guidelines for these drugs (36).

There are several limitations to the present study. Firstly, the study was observational and was designed as a cost-identification project rather than a cost-efficiency or a cost-benefit project. Additionally, 'cost,' in general, may comprise cost of administration, cost of equipment and, staff, cost with respect to quality of life of the patient and other intangible costs such as absence from workplace and stress which were not calculated in the present study (37). Because of the shorter duration of the study, follow-up of the patients with respect to their overall morbidity and the calculation of quality of life-years gained were not done.

In conclusion, our findings suggest that the use of sedation, analgesia and neuromuscular blockade in patients admitted to ICU has a major pharmacoeconomic impact, accounting for more than 50% of ICU drug costs. Therefore, there is a need for formulating and implementing guidelines and protocols to facilitate appropriate utilization of these drugs.

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