■ ECONOMICS

Economic Evaluation of Propofol for Sedation of Patients Admitted to Intensive Care Units

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Background: The goal of the current study was to evaluate the economic impact of propofol as compared with midazolam for sedating patients in the intensive care unit (ICU).

Methods: A randomized, unblinded, multicenter pharmaco-economic trial captured health resource utilization and outcome measurements associated with sedation and treatment of patients in four ICUs across Canada. Statistical analysis was performed to investigate the difference in sedation quality, ICU length of stay, and other health resources used. The authors compared the costs (1997 Canadian dollars) associated with the two treatments. Two types of sensitivity analyses were performed.

Results: Although overall sedation duration was similar, propofol patients spent more time at adequately sedated status (60.2% *vs.* 44%; *P* = 0.01) and were extubated faster (median extubation time, 2.5 *vs.* 7.1 h; *P* = 0.001). The ICU length of stay and health resource utilization did not differ. The total cost per patient, including drug cost and ICU stay cost, did not differ between groups (median, $5,718 for propofol *vs.* $5,950 for midazolam; *P* = 0.94). The first sensitivity analysis suggested that the incremental cost (per patient) of propofol varies from an extra cost of $114 to a savings of $2,709. Based on a hypothetical model, the second sensitivity analysis showed a potential saving of $479 per patient as a result of improved discharge planning.

Conclusion: The analysis demonstrated that using propofol resulted in a reduction of time to extubation and higher sedative regimen costs. There was no difference in intensity of resource use or ICU length of stay and hence in costs. Issues regarding discharge delay among propofol-treated patients remain to be explored.

IN an intensive care unit (ICU), sedation is frequently required for critically ill patients to minimize the impact of a variety of noxious stimuli and to improve their tolerance to mechanical ventilators. Given an increasing demand for ICU beds, a sedative agent that permits rapid recovery of cognition and spontaneous respiration is desirable. As an intravenous sedative, propofol has been compared with midazolam for sedation of ICU patients from both a clinical and cost-effectiveness point of view. When both are administered by continuous intravenous infusion, there is evidence that propofol is associated with a more favorable sedation quality.[1–3] Propofol possesses some of the ideal sedation agent characteristics with its rapid recovery feature (resulting earlier time to extubation),[1–7] although one study demonstrated no time difference.[8] As compared with midazolam, the economic disincentive of using propofol is its higher acquisition cost.[9–12] Furthermore, cost-effectiveness studies of propofol provide conflicting evidence.[8,9,12] *A priori*, the question that remains unanswered is whether an overall reduction of hospitalization expenditure would be a cost offset to the increased drug cost associated with propofol use. Hence, in this study, we prospectively evaluated the economic impact of propofol relative to midazolam by considering all treatment-related costs, including incremental drug and hospitalization costs.

The objective of this study was to characterize ICU sedation times, sedative costs, and other healthcare resource use to estimate the economic impact of adopting propofol in ICUs in Canada.

Materials and Methods

A multicenter, randomized, open-label trial was conducted between September 1994 and June 1995 in four academic medical centers across Canada.[13] The four institutions were Queen Elizabeth II Health Sciences Center (Halifax, Nova Scotia), Foothills Hospital (Calgary, Alberta), Ottawa General Hospital (Ottawa, Ontario) and Vancouver General Hospital (Vancouver, British Columbia). The research review board of each institution approved the protocol and consent process. To be eligible for the study, patients had to be aged 18 yr or older and had to require sedation with propofol or midazolam as a primary sedative agent when being mechanically ventilated. Exclusion criteria were known or suspected allergy to propofol or midazolam, suspected or known pregnancy, coma caused by cerebrovascular accident or of unknown cause, and uncontrolled seizures defined as *status epilepticus*—seizures following one another with no intervening periods of consciousness. Consent was obtained from the patients or their

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next of kin once they were admitted into the ICU and met the study eligibility criteria.

For analytical convenience, ICU length of stay was divided into three consecutive time periods. Period I was the interval between ICU admission and beginning of sedation. Period II was the interval from the beginning of sedation to sedation termination and extubation. Period III was the interval between extubation and discharge from the ICU. During period I, administrative tasks were performed in preparation for initiation of sedation. In period II, primary ICU activities such as sedation and extubation were performed. Period III was focused on discharge planning.

Baseline measurements collected during period I included patient demographics, ICU admission diagnosis, body temperature and weight, heart rate, blood pressure, and respiratory rate. Within the first 24 h of ICU admission, Acute Physiology and Chronic Health Evaluation II and Therapeutic Intervention Scoring System scores were calculated to assess severity of disease and therapeutic interventions, respectively.[14,15] During period II, to evaluate the sedation adequacy, a desired sedation target was determined for individual patients by the attending physician using the Ramsay scoring scheme.[16] Sedation status was defined as insufficient if the Ramsay score was below the target, adequate if the score was at the target, and excessive if the score was above the target. For both drugs, sedation was induced slowly with a continuous infusion to titrate to the desired clinical effect and minimize the risk of hypotension. For propofol patients, initiation of sedation was at $3\text{--}6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and increased or decreased until the target Ramsay level was achieved. Similarly, midazolam patients received the dose initially at the rate of $0.012 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ with increments or decrements subsequently to reach the appropriate Ramsay sedation score. The Ramsay score was monitored every 5 min for 20 min at induction and subsequently every hour during maintenance by nurses. The overall sedation adequacy was determined according to the cumulative number of hours under each of the three sedation levels defined above. Based on clinical judgment, various critical interventions, including beginning of sedation, weaning, termination of sedation, and extubation (ready and actual), were performed, and corresponding time points were recorded. Three sedation dosage-related measures were collected during the sedation process: the total sedative drug quantity supplied (including wastage), cumulative sedative dosage when the degree of sedation first reached the target level, and the actual quantity of drug required to maintain the sedation desired. Finally, at period III, ready and actual discharge intervals were recorded, indicating the last stage of ICU stay.

During the study, the use of all healthcare resources was prospectively recorded at the bedside by the attending nurse and reviewed by a nurse study coordinator during the entire ICU length of stay. Variables recorded included ICU physician visits, nursing time, other health professional contacts, diagnostic tests, and medications. Physician visits were recorded according to specialty and type of visit. Physician specialty included ICU physician, ICU fellow, ICU resident, anesthesiologist, respirologist, surgeon, and other. Physician visits included initial assessment, subsequent visits, procedures, and other types of visit e.g., family interviews. The duration of physician visits was not recorded because physicians were paid per visit–consult according to a time-independent fixed payment schedule. Nursing time (minutes), including that required of the primary nurse and any assisting nurse, was recorded. Nursing time included caring time, charting time, time for making care decisions, and time spent on conferring with the patient's family. Other health professional contacts reflected services delivered in respect of physiotherapy and respiratory and nutritional therapy. Each consultation was recorded in terms of specialty and duration. All concomitant medications (nonsedative) during ICU stay were recorded according to quantity and route of administration, i.e., nonintravenous, intravenous, or intramuscular medications and intravenous infusion solutions, respectively. Frequency and type of hematology, microbiology, and chemistry tests performed during patient ICU stay were also prospectively recorded.

Statistics

Univariate comparison of patient characteristics was based on data collected during period I. Individual segments of ICU length of stay were analyzed. Because period II was the core period spent in the ICU, we performed more detailed analysis assessing the relative efficacy of sedative regimes. Wilcoxon nonparametric test was applied to compare the length of ICU stay between the two treatment groups.

Cost Estimation and Sensitivity Analysis

The following equation describes the incremental cost calculation:

$$\text{incremental cost} = \Delta \text{CICU-stay} + \Delta \text{CRx}$$

where $\Delta\text{CICU-stay}$ is the incremental cost of ICU stay and ΔCRx is the incremental sedative drug cost. $\Delta\text{CICU-stay}$ is the incremental difference in ICU length of stay with fixed ICU daily cost and is estimated by the difference in the length of stay multiplied by the fixed daily unit cost. ΔCRx was estimated by applying the hospital acquisition cost for propofol and midazolam to the recorded total drug usage (including wastage) for patients in each study arm. All costs were in 1997 Canadian dollars.

The fixed ICU daily cost was estimated from the Saint Paul's Hospital Cost Model. The Saint Paul's Hospital

Table 1. Health Services Utilization

	Midazolam [Mean (SD)]	Propofol [Mean (SD)]	P Value
Physician visits (times/h)	0.27 (0.17)	0.31 (0.21)	0.23
Nursing time (min/h)	26.5 (9.7)	27.2 (10.0)	0.73
Other health professional visits (min/h)	11.1 (7.8)	11.2 (8.2)	0.94
Diagnostic tests (times/h)	1.6 (0.7)	1.5 (0.7)	0.40
Medication (times/h)	1.1 (1.5)	1.3 (2.1)	0.58

Cost Model provides fully allocated unit costs for all services and expenditures within the hospital, including overhead, opportunity cost of resources, including fixed assets, as well as global depreciation at 5% of capital equipment. The cost model and the methodology of simultaneous allocation is described in detail elsewhere.[17] The resulting "fully allocated" unit costs are according to the appropriate output for each department that was often a Work Load Measurement Unit, a standardized output reporting mechanism implemented by Statistics Canada.[18] The cost of bed, physician, nursing, house keeping, mechanical ventilation, and other commonly used equipment–interventions in the ICU were included in the unit cost calculation.

Two types of sensitivity analyses were conducted. One was to estimate the uncertainty of costs/savings that may be attributable to potential estimation error of the length of stay cost and sedative drug cost. The other sensitivity analysis was based on a hypothetical model that examined the potential cost savings of propofol assuming better discharge planning, such that there is no difference in the discharge times between treatments once patients were extubated. Analyses of covariance were conduced with log-transformed dependent variables, sedation drug cost, and extubation time, respectively, to satisfy the normality assumption of the statistical methodology.

Results

A total of 156 patients were enrolled in the study: 79 and 77 patients were randomized to the midazolam and propofol groups, respectively. There were 11 deaths in the midazolam group (13.9%) and 15 deaths (19.5%) in the propofol group ($P = 0.37$). Sedation failure (defined

Table 2. Sedation Status*

Sedation Status (%)	Midazolam	Propofol	P Value
Insufficient	8.1	11.2	0.29
Adequate	44.0	60.2	0.01
Excessive	18.4	12.0	0.12
Undefined status	29.5	16.6	0.01

* Status: Percent attributes to the period from beginning to termination of sedation.

Table 3. Median ICU Length of Stay (h)

	Midazolam	Propofol	P Value
Period I: sedation preparation			
Admission to beginning of sedation	3.0	2.7	0.81
Period II: sedation and extubation			
Beginning of sedation to reduction	17.5	13.9	0.44
Reduction to termination of sedation	1.1	0.9	0.46
Termination to ready for extubation	7.1	2.5	0.001
Ready for extubation to actual extubation	0.4	0.3	0.31
Total in period II	30.3	21.5	0.08
Period III: discharge planning			
Actual extubation to ready for discharge	21.5	22.7	0.19
Ready for discharge to actual discharge	4.3	3.8	0.47
Total in period III	26.0	26.5	0.35
Total ICU length of stay	72.7	69.8	0.94

ICU = intensive care unit.

as the inability to achieve target sedation levels appropriate for the patient according to the Ramsay score or because of the occurrence of a serious adverse reaction) occurred in four midazolam-treated patients (one of whom died) and seven propofol-treated patients (four of whom died) ($P = 0.30$). For the remaining 124 patients (65 midazolam, 59 propofol) who survived and were discharged from the ICU, no difference was found in age (mean, 59.8 *vs.* 60.3 yr; $P = 0.82$). There were more women in the midazolam group (45% *vs.* 27%; $P = 0.05$) with a tendency to a lighter weight distribution. No differences between groups were found for baseline hemodynamic parameters of blood pressure, heart rate, respiratory rate, or arterial blood gases.[13]

Tracheal extubation occurred while continuous sedation was ongoing in 25 patients (12 midazolam and 13 propofol), preventing ascertainment of the termination of sedation to extubation time interval. Data for the primary outcome variables for the remaining 99 patients were further analyzed.

Table 1 summarizes the hourly health resources used during patients' ICU stay. There were no significant differences in frequency of physician visits, nursing time, or other health professional visits between groups. There were also no differences with respect to the frequency of clinical tests and nonsedative medication use.

Table 2 shows the comparison of sedation adequacy between propofol and midazolam groups. Propofol-treated patients spent more time at the targeted Ramsay sedation score (mean, 60.2% *vs.* 44.0%; $P = 0.01$).

Table 3 presents ICU length of stay (median) according to the three time periods (period I, period II, and period III) defined previously. Marginally significant differences

Table 4. Analysis of Covariance*

	Extubation Time		Sedative Drug Cost	
	Coefficient	P Value	Coefficient	P Value
Constant	0.58	0.02	4.61	0.001
Treatment effect (TE) Propofol *versus* midazolam	−1.43	0.001	1.27	0.001
Sedation time (ST)	0.003	0.04	0.007	0.001
Interaction TE × ST Propofol *versus* midazolam			−0.005	0.02

* Both extubation time and sedative drug cost were log-transformed.

between groups were found in time in period II (propofol 21.5 *vs.* midazolam 30.3 h; $P = 0.08$). No significant differences were found in other periods and the total ICU length of stay (propofol 69.8 *vs.* midazolam 72.7 h; $P = 0.94$). Further analysis of time segments within each period showed that the time interval from sedation termination to ready for extubation was significantly less for the propofol group (median 2.5 *vs.* 7.1 h; $P = 0.001$).

The fully allocated hotel cost of ICU stay was estimated as $1,965 per patient per day from the Saint Paul's Hospital Cost Model. There was no significant difference in ICU stay cost (median, $5,718 for propofol *vs.* $5,950 for midazolam; $P = 0.94$) between the two groups as no difference was found in the overall length of stay. Sedative costs, which were calculated based on the recorded drug quantity, including wastage per patient and the respective drug price (propofol, $43.01, 1,000 mg/100 ml; midazolam, $20.21, 50 mg/10 ml), were higher for patients in the propofol group (median, $86.02 *vs.* $40.42; $P = 0.08$). The wastage rates were similar (propofol 57% *vs.* midazolam 60%; $P = 0.51$). The total costs, including ICU stay costs and sedative drug costs, did not differ between groups (median, $5,765 for propofol *vs.* $5,998 for midazolam; $P = 0.94$) and yielded to a net saving of $233 per patient for propofol. The sensitivity analysis using the total costs at the 25th and 75th percentile suggested that the incremental cost of propofol varied from an extra cost of $114 per patient to a savings of $2,709 per patient.

We further considered a hypothetical model that assumed that time from extubation to ICU discharge was equivalent for the two groups. The savings as a result of reduced length of stay are important to estimate regardless of whether ICU staff requirement actually changes as a result. This is so because other patients can use the ICU beds that become available as a result. We first modeled the log-transformed sedation extubation time and sedative drug cost as dependent variables adjusted by duration of sedation (sedation beginning to termination). Our analysis (table 4) suggested that extubation time for the propofol group was 4.2 times (95% confidence interval, 2.3, 7.5) shorter than for the midazolam group. The extubation time was also positively associated with the duration of sedation at a significance level of 0.05. Propo-

fol costs per patient were 3.6 times (95% confidence interval, 2.4, 5.3) higher than midazolam, and sedative drug cost was positively associated with the sedation duration as well.

We further applied the results in table 4 to calculate the incremental cost components, ΔCICU-stay and ΔCRx. The model predicted that for a patient who needed 10 h of sedation, using propofol would lead to an incremental lessening of extubation time by 5.9 h and an incremental drug acquisition cost of $76 compared with midazolam. Under the assumption of equivalent time from extubation to ICU discharge, the reduction of time to extubation would lead to a shorter ICU length of stay, and the resulting potential savings were estimated to be $479 per patient. Combining this amount with incremental sedative cost, the net saving was calculated to be $403. The sensitivity analysis demonstrated that the potential savings could vary between $244 and $570 per patient when both ICU daily cost and extubation reduction times were varied within the range of ± 30%. Furthermore, as the duration of sedation increased, the potential savings by using propofol increased.

Discussion

This randomized unblinded trial confirmed that propofol was more effective compared with midazolam with respect to quality of sedation among critically ill patients admitted to the ICU. However, healthcare resource use did not differ across treatment groups. The analysis showed that, given the current management of patients in ICUs, there was a significant shortening of time between termination of sedation and extubation when propofol was used, but this did not translate into a lessening of the overall observed duration of stay in an ICU for patients receiving propofol compared with those receiving midazolam. As a result, there was no difference between the treatment groups in the total sum of ICU stay cost and sedative drug cost.

In our sensitivity analysis, where we assumed that time from extubation to ICU discharge was equivalent for patients treated with either propofol or midazolam, a potential cost savings of $403 would be achievable by using propofol instead of midazolam for every 10 h of sedation time. It is important to note that this savings estimate is "modeled" and not "observed" in this trial. Furthermore, the success–magnitude of the modeled impact would be dependent on the design of optimal discharge criteria (only one component of which would be rapid tracheal extubation). The results from our sensitivity analysis led to our speculation of why ICU discharge was delayed. It could be caused by problems in the systematic handling of patients within these hospitals. For example, routine difficulties associated with discharging patients form ICU because of problems such

as a lack of floor beds to receive these transferred patients would eliminate any pharmacokinetic advantage to earlier tracheal extubation associated with propofol use. On the other hand, patients treated with propofol, although extubated earlier (and perhaps prematurely), may have required more ongoing care in the ICU than patients treated with midazolam.[13] The degree to which these aspects might have contributed to the results remained to be studied.

There are several similarities between our findings and those of Carrasco *et al.*,[9] the only other study published to date that performed a similar comparison on a Spanish ICU population with respect to sedation quality and cost between these two drugs. There are, however, some important differences. Although our study shows no difference in actual ICU length of stay in favor of either drug, Carrasco *et al.* showed that the sum of "time up to extubation" and "total recovery time" were always less for propofol relative to midazolam. In our analysis, we were able to show that, although extubation time was dependent on sedation duration for both sedative drugs, extubation time with propofol is 4.2 times faster. Both studies imply that with propofol, one can be assured of a rapid and predictable recovery time.

One limitation of this study is the lack of treatment masking, which might lead to potential bias with respect to clinicians' assessment of the sedation quality and the duration of intubation. However, we believe that the practicality of masking the treatment in our study was limited. The physical appearances of these two drugs were different. In addition, knowledgeable caregivers can recognize the treatments by the differences in the onset of drug effect. Furthermore, masking infusions by wrapping bags and tubes at all hours was not practical. Details were reported elsewhere.[13]

Another difficulty we encountered was that we were unable to cost all the nonsedative drugs and diagnostic tests performed in the ICU. Another limitation of the study was the absence of a quality-of-life measurement from the patient's perspective. Thus, there were no measurements of adverse events commonly experienced by ICU patients such as pain, nausea, vomiting, or other incidents to evaluate patient's perception and satisfaction of the ICU experience.

The study design adopted for this trial was in the tradition of prospectively collecting economic data alongside clinical data.[19] Such designs often create tension between internal and external validity,[20] and our study team had to grapple with some of these issues. Some of the important lessons that we learned and that might be important for other researchers contemplating such pharmacoeconomic studies are noted. In a setting such as an ICU, where care is highly resource intensive, the ability to measure reduced resource use as a result of the use of one type of drug over another is critically important, yet is itself an expensive activity because additional data collection resources are required. Therefore, study investigators need to prioritize the importance of collecting each variable prospectively and consider the trade-off of reduced precision *versus* ease of retrospective data collection from secondary sources such as medical charts routinely completed. Given that we found that the intensity of medical resources used did not vary across treatment arms, the prospective measurement of physician visit, nursing intensity, and other consults could have been avoided if lesser importance had been placed *a priori* on collecting such data and the focus had instead been on capturing only the difference in overall length of stay. As a general rule, to facilitate ease of data collection, only data that would otherwise not be collected should be collected prospectively.

The study showed that overall ICU length of stay and costs remained the same for both midazolam and propofol treatment groups, and for the propofol subjects, the time reduction gained from early extubation was counterbalanced by the prolonged time waiting for ICU discharge. Whether such discharge delay is a result of propofol-treated patients requiring more ongoing care in the ICU or the lack of efficiency in the institutions participating in the study is not clear, and this issue should be explored in future studies.

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Appendix: Propofol Study Group

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