Cost effectiveness of aggressive care for patients with nontraumatic coma*

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Objective: To estimate the cost effectiveness of aggressive care for patients with nontraumatic coma.

Design: Cost-effectiveness analysis.

Setting: Five academic medical centers.

Patients: Patients with nontraumatic coma enrolled in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT). Patients with reversible metabolic causes of coma such as diabetic ketoacidosis or uremia were excluded.

Measurements: We calculated the incremental cost effectiveness of withholding cardiopulmonary resuscitation and ventilatory support after day 3 of coma. We estimated life expectancy based on up to 4.6 yrs of follow-up. Utilities (quality-of-life weights) were estimated using time-tradeoff questions. Costs were based on hospital fiscal data and Medicare data. Separate analyses were conducted for two prognostic groups based on five risk factors assessed on day 3 of coma: age $\geq 70$ yrs, abnormal brainstem response, absent verbal response, absent withdrawal to pain, and serum creatinine $\geq 132.6 \text{ mol/L} (1.5 \text{ mg/dL})$.

Results: For the 596 patients studied, the median (25th, 75th percentile) age was 67 yrs (range, 55–77), and 52% were female. By 2 months after enrollment, 69% had died, 19% were severely disabled, 7% had survived without severe disability, and 4% had survived with unknown functional status. The incremental cost effectiveness of the more aggressive care strategy was $140,000 (1998 dollars) per quality-adjusted life year (QALY) for high-risk patients (3–5 risk factors, 93% 2-month mortality) and $87,000/QALY for low-risk patients (0–2 risk factors, 49% mortality). In sensitivity analyses, the incremental cost per QALY did not fall below $50,000/QALY, even with wide variation in our baseline estimates.

Conclusions: Continuing aggressive care after day 3 of nontraumatic coma is associated with a high cost per QALY gained, especially for patients at high risk for poor outcomes. Earlier decisions to withhold life-sustaining treatments for patients with very poor prognoses may yield considerable cost savings. (Crit Care Med 2002; 30:1191–1196)

KEY WORDS: coma; cost effectiveness; medical decision making; outcomes; costs cardiopulmonary resuscitation

Outcomes for patients with nontraumatic coma are generally poor; the majority of patients die within 1 month, and a substantial proportion of survivors are left with severe functional impairments (1–3). Families and physicians often face difficult decisions about whether and when to limit expensive and invasive life-sustaining treatments.

The cost effectiveness of aggressive care for nontraumatic coma has not been studied.

We anticipated that the incremental cost effectiveness of aggressive treatment strategies for nontraumatic coma would vary according to patients’ baseline prognoses. Previously, we had identified risk factors associated with poor outcomes and developed a prognostic system to identify patients who are unlikely to survive (1). For our present analysis, we studied a cohort of patients hospitalized with nontraumatic coma (excluding more reversible causes of coma such as diabetic ketoacidosis and uremia) and used our prognostic model to divide patients according to their risk of short-term mortality. Within each prognostic group, we divided patients based on whether decisions had been made by day 4 of coma to withhold cardiopulmonary resuscitation (CPR) and ventilatory support (i.e., whether patients had do-not-resuscitate [DNR] and do-not-intubate orders) and estimated the incremental cost effectiveness of continuing aggressive treatment vs. withholding CPR and ventilatory support.

METHODS

Overview

We compared the costs and outcomes of two treatment strategies for patients with

*See also p. 1382.
nontraumatic coma: a) a less aggressive treatment strategy involving a decision by day 4 of coma to withhold CPR and ventilatory support (i.e., DNR orders had been written) and b) a more aggressive treatment strategy, which did not include a plan to limit these life-sustaining treatments. We stratified patients according to an objective assessment of their prognoses and estimated the incremental cost effectiveness of the more aggressive treatment strategy compared with the less aggressive treatment strategy.

Patient Population

This cost-effectiveness analysis is based on data from patients with nontraumatic coma enrolled in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT), a prospective study of outcomes, preferences, and decision making for seriously ill hospitalized adults. Full descriptions of the objectives and methods of SUPPORT have been published previously (4, 5). Briefly, inpatients were enrolled prospectively from June 1989 through January 1994 at five academic medical centers. Institutional review boards of the participating hospitals approved the study design, and informed consent was obtained orally before interviews with patients, their families, and their physicians. SUPPORT had two phases: an observational phase and an interventional phase. During the interventional phase, clinicians randomized to the intervention were given information about patients' prognoses and preferences for care, and nurses facilitated communication between patients and clinicians. Because the intervention did not affect mortality or resource use (5), patients from both phases and from both the intervention and control groups were included in our analysis.

Patients were eligible for SUPPORT if they were ≥18 yrs and met criteria for at least one of nine diagnostic categories (4), one of which was nontraumatic coma. Patients who were discharged from the hospital or who died within 48 hrs of study entry were excluded from SUPPORT. Patients were included in the coma category if during the first 24 hrs of their hospitalization or while receiving care in the intensive care unit they were described by a physician as “comatose,” “unconscious,” or “obtunded” and had a Glasgow Coma Score ≤9 for ≥6 hrs (2, 6). Patients were excluded if trauma, drug intoxication, hypothermia, or an operative complication was the primary cause of coma. Patients were also excluded if they had any of the following metabolic causes of coma: diabetic ketoacidosis, nonketotic hyperosmolar syndrome, thyrotoxicosis, myxedema, hepatic encephalopathy, uremia, hypotnatremia, hypernatremia, hypercalcemia, or hyperglycemia or hypoxemia were included.

Data Collection

Research nurses reviewed medical records throughout patients' hospitalizations and abstracted patients' diagnoses and comorbid conditions. They also recorded data for calculating the Therapeutic Intervention Scoring System score (7) on study days 1, 3, 7, 14, and 25. The Therapeutic Intervention Scoring System is a measure of resource intensity that assigns one point for minor interventions (such as pulse oximetry or peripheral intravenous therapy) and two to four points for more substantial interventions (such as intubation or surgery). Comorbid conditions (such as diabetes mellitus, congestive heart failure, and stroke) were abstracted using a list developed as part of the Acute Physiology and Chronic Health Evaluation II scoring system; a comorbidity score was calculated by a simple count of comorbid conditions (8). Nurses reviewed hospital charts to determine whether decisions were made to withhold CPR or ventilatory support.

Trained interviewers interviewed patients and their surrogates to obtain information on patients' functional status (as measured by a modified version of the Katz Activities of Daily Living Scale) (9, 10) and utilities (see below). The surrogate was defined as the person who would make decisions on the patient's behalf if the patient were unable to do so. Patients were excluded from interviews if they were unable to communicate because of coma, having an endotracheal tube, cognitive impairment, or other reasons.

Analytic Methods

Descriptive Statistics and Prognostic Model. To characterize patients at baseline and at the 2-month follow-up, we tabulated frequencies for categorical variables and calculated median and 25th and 75th percentiles for continuous variables. Statistical analyses were performed using SAS (SAS Institute, Cary, NC). Using a prognostic model we previously developed and validated (1), we stratified patients into two groups based on their risk of dying within 2 months. The prognostic model assigns one point for each of the following five risk factors on day 3 of coma: age ≥70 yrs, abnormal brainstem response, absent verbal response, absent withdrawal to pain, and serum creatinine level ≥132.6 μmol/L (1.5 mg/dL). Based on the 222 patients used to derive the prognostic model, predictions of 2-month mortality according to number of risk factors were as follows: zero risk factors, 20%; one risk factor, 33%; two risk factors, 60%; three risk factors, 97%; four risk factors, 96%; and five risk factors, 100%. For the purpose of this cost-effectiveness analysis, we defined the high-risk group as having three to five risk factors and the low-risk group as having zero to two risk factors.

To determine whether differences in patients' prognoses within the two prognostic strata (0–2 vs. 3–5 risk factors) guided treatment decisions, we compared the mean number of risk factors for patients who were treated aggressively with those for whom decisions were made by study day 4 to withhold CPR and ventilatory support. To examine whether our definition of aggressive care captured differences in intensity of treatment, we compared day 7 resource intensity (Therapeutic Intervention Scoring System) scores according to whether patients had DNR and do-not-intubate orders.

Utilities. In cost-effectiveness analyses, utilities (quality-of-life weights) are used to adjust quantity of life for its quality and to allow years spent in health states associated with worse quality of life to be valued less than health states associated with better quality of life. Utility scores have values from zero to one, with higher scores indicating better quality of life. The years of life gained by a particular medical intervention are multiplied by the utility associated with those years to estimate the quality-adjusted life years (QALYs) gained by that medical intervention.

We used patients' and surrogates' responses to time-tradeoff questions asked during interviews at the 6-month follow-up to estimate their utilities (11–13). For the time-tradeoff questions, interviewers asked patients to state the amount of time in excellent health they would equate with living 12 months in their current state of health. For example, a patient willing to trade 12 months in his current health for no less than 6 months in perfect health would have a utility of 0.5 (6/12). For our baseline analysis, we assumed that the utilities reported by interviewed patients and surrogates at the 6-month follow-up represented those of all patients for their remaining months or years, and we used the overall mean value to quality-adjust life expectancy for both risk groups.

Healthcare Costs. Charges for the index hospitalizations were collected from the participating hospitals' billing systems. We estimated hospital costs by adjusting charges using Medicare cost-to-charge ratios for Uniform Bill 1982 (UB82) cost centers at each participating hospital. We focused on the cost of the index hospitalization incurred after study day 3 because our analyses compared costs and outcomes experienced after the decisions made by study day 4 concerning whether to withhold resuscitation and ventilatory support. We used primary data to estimate costs separately according to risk group and treatment strategy.

We linked Medicare financial data (Parts A and B) with SUPPORT data to estimate hospitalization costs after the index hospitalization and to estimate physician costs during and after the index hospitalization. We assumed...
that costs for patients without Medicare insurance (i.e., most patients <65 yrs) were similar to those of patients covered by Medicare. We estimated physician costs using Resource-Based Relative Value Scale methodology (14). We estimated annual hospital and physician costs after year 1 based on costs incurred during the final quarter of year 1.

We assumed that patients with four or more dependencies in activities of daily living were severely disabled (1) and would require long-term care. (For high-risk patients, 94% had four or more dependencies in the Activities of Daily Living Scale, and 70% of low-risk patients had four or more dependencies; therefore, we assumed that these percentages of survivors would require long-term care.) We estimated the annual cost of long-term care based on the Tung et al. (15) estimate of the costs of institutional care for patients who were severely disabled after suffering a stroke. Their estimate was within $300 dollars of an estimate made by Leon and colleagues (16) of the costs of institutional care for patients who were severely disabled after suffering a stroke. We added $200 dollars to our estimate to adjust for inflation through 1998 dollars using the medical component of the Consumer Price Index. Our analyses only considered healthcare costs and did not attempt to estimate additional societal costs or savings.

For physician and hospital costs for the index hospitalization, we used primary data to make separate estimates based on risk group and treatment strategy. For hospital and physician costs from discharge after the index hospitalization through 1 yr, we made separate estimates for each risk group, but assumed that costs would be the same for each treatment strategy. For hospital, physician and institutional care costs after year 1, we used one estimate for all patients and assumed that costs would not differ by risk group or treatment strategy.

Calculating Costs per Quality-Adjusted Life-Year. Cost-effectiveness analysis is a tool that estimates the healthcare costs and health benefits associated with various medical interventions. The benefits are measured in gains in quantity and quality of life and are expressed as QALYs. Cost-effectiveness ratios (expressed as dollars per QALY gained) represent the additional costs and additional quality-adjusted life expectancy associated with one medical treatment compared with a less effective treatment. We calculated the following ratio to evaluate the cost effectiveness of aggressive care vs. withholding CPR and ventilatory support:

\[
\frac{\text{Cost} \; \text{of} \; \text{more} \; \text{aggressive} \; \text{care}}{\text{QALY}} = \frac{\text{Cost} \; \text{of} \; \text{less} \; \text{aggressive} \; \text{care}}{\text{QALE of} \; \text{more} \; \text{aggressive} \; \text{care}} - \frac{\text{QALE of} \; \text{less} \; \text{aggressive} \; \text{care}}{\text{QALE of} \; \text{less} \; \text{aggressive} \; \text{care}}
\]

where QALE is quality-adjusted life expectancy.

We conducted our cost-effectiveness analyses from a societal perspective. Cost-effectiveness analyses were done using DATA 3.0 (TreeAge Software, Williamstown, MA). We used Markov models (17) to estimate expected lifetime costs and quality-adjusted life expectancy for each strategy (i.e., aggressive care vs. withholding CPR and ventilatory support). A Markov model tracks a cohort over time until the entire cohort has died. The model requires specification of the probability of dying each year (i.e., 1-yr mortality estimates). We estimated life expectancy based on complete follow-up of SUPPORT patients through December 31, 1994, using the National Death Index. Our mortality estimates for years 1, 2, and 3 were derived directly from Kaplan-Meier curves for SUPPORT patients. Mortality estimates for year 1 were made for each risk group, broken down by treatment strategy. Annual mortality after year 1 was based on a survival curve for all patients because there was not a sufficient number of survivors to make separate estimates according to risk group or treatment strategy. Therefore, we made the simplifying assumption that survival after year 1 was not related to risk group or initial treatment strategy. We estimated mortality after year 3 by summing disease-specific mortality (i.e., excess mortality associated with having a history of nontraumatic coma) and age-specific mortality (i.e., the background mortality expected if patients did not have nontraumatic coma). Age-specific mortality was based on U.S. life tables (18). Note that age-specific mortality increases each year as the cohort ages. We estimated disease-specific mortality from mortality observed in year 3 of SUPPORT. (Data after year 3 were not used due to flattening of the survival curves and small sample size after year 3.) We isolated disease-specific mortality from total mortality by subtracting out age-specific mortality in year 3. We assumed that disease-specific mortality would remain constant in subsequent years. To estimate total mortality for each year after year 3, we added disease-specific mortality to age-specific mortality.

To estimate the total cost of each treatment strategy for each prognostic group, we summed the mean hospital and physician costs for the index hospitalization, mean hospital and physician costs from discharge through 1 yr of follow-up, mean annual hospital and physician costs after year 1 (based on Part A and B Medicare costs for quarter 4 of year 1), and mean annual cost of long-term care.

We discounted all costs and quality-adjusted years at a rate of 3% per year (19). We calculated the incremental cost effectiveness in 1998 dollars per quality-adjusted life-year (QALY) gained of the more aggressive vs. the less aggressive treatment strategy for each of the two risk groups. We rounded incremental cost-effectiveness ratios to two significant figures.

Sensitivity Analyses

We performed sensitivity analyses to assess how different assumptions would affect our results. In one-way sensitivity analyses, we individually varied each of our cost estimates and our estimate for annual mortality after year 1 from 50% to 200% of our baseline estimates. In addition, we varied the utilities from 0.5 to 1.0 and the discount rate from 0% to 10%. We also performed modified best- and worst-case three-way sensitivity analyses, where we simultaneously varied the three variables to which our results were most sensitive (annual mortality after year 1, year 1 healthcare costs, and annual costs after year 1). To bias our analysis toward finding more favorable cost-effectiveness ratios, we simultaneously lowered these three estimates to 67% of our baseline values, and to bias our analysis toward finding less favorable ratios, we simultaneously increased these three estimates to 150% of our baseline values.

RESULTS

Patients’ Baseline Characteristics and Outcomes. Within 2 months after enrollment, 413 of the 596 patients with nontraumatic coma (69%) had died, 115 (19%) were severely disabled (4–7 dependencies in Activities of Daily Living Scale), six (1%) had survived with mild-moderate disability (2–3 dependencies), 37 (6%) had survived with no or mild disability (0–1 dependencies), and 25 (4%) had survived with unknown functional status (Table 1). Information about the five risk factors included in the prognostic model was available for 549 patients: 290 (53%) had zero to two risk factors and were classified as low-risk, and 259 (47%) had three to five risk factors and were classified as high-risk. By study day 4, decisions were made to withhold CPR and ventilatory support (i.e., the less aggressive care strategy was undertaken) for 40 (14%) of the 290 low-risk patients and for 81 (31%) of the 259 high-risk patients. For high-risk patients, the mean number of risk factors was similar for patients who were treated aggressively vs. those not treated aggressively, suggesting that DNR orders were not a marker for poorer prognosis (mean number of risk factors 3.6 for patients treated aggressively and 3.5 for patients who had DNR orders). For low-risk patients, those who had a DNR order had modestly worse prognoses, with a mean number of risk...
factors of 1.6 compared with 1.3 for those in the aggressive care strategy ($p = .005$). The two care strategies we defined based on decisions to withhold CPR and ventilatory support described groups of patients who received different intensities of treatment. For low-risk patients, the mean day 7 resource intensity (Therapeutic Intervention Scoring System) score was 12.0 for those who were DNR/do-not-intubate by day 4 and 27.7 for those who were not ($p = .0001$). For high-risk patients, the mean resource intensity score was 14.9 compared with 26.2 ($p = .003$). First-year costs were considerably higher for patients who were treated aggressively (Table 2).

Two-month mortality was 49% for low-risk patients and 93% for high-risk patients (Fig. 1). For low-risk patients, 1-yr mortality was 58% for patients receiving more aggressive care and 95% for patients receiving less aggressive care. For high-risk patients, 1-yr mortality was 95% for patients who received more aggressive care and 99% for patients receiving less aggressive care. Based on all patients who survived at least 1 yr (not divided according to treatment strategies or risk group), the annual disease-related mortality after year 1 was estimated to be 7.5%.

Of patients who survived at least 6 months, 31 patients and 70 surrogates provided data on patient utilities. The mean utility for this group was 0.68.

Cost-Effectiveness Analyses: Baseline Case. The incremental cost per QALY gained of providing aggressive care rather than withholding CPR and ventilatory support by day 4 of coma was $140,000 (1998 dollars). For patients with better prognoses (0–2 risk factors), the incremental cost was $87,000/QALY. These ratios are considerably higher than cost-effectiveness ratios for many other commonly used medical interventions. For example, coronary artery bypass surgery rather than medical therapy for left main coronary artery disease costs about $9,500/QALY (1998 dollars) (20, 21), medical therapy for severe hypertension costs about $28,000/QALY (1998 dollars) (21, 22), and treatment with t-PA rather than streptokinase for myocardial infarction costs about $39,000 per year of life saved (1998 dollars) (23).

Previous cost-effectiveness analyses have demonstrated that the cost effectiveness of aggressive treatment strategies for patients hospitalized with serious illness is dependent on patients’ baseline prognoses. In analyses using similar methods and also based on data from SUPPORT, we determined the cost effectiveness of aggressive treatment for patients with acute respiratory failure who require ventilatory support and for patients with renal failure requiring dialysis. For patients with acute respiratory failure at highest risk for short-term mortality (<50% probability of surviving at least 2 months), ventilator support and intensive care costs more than $100,000 per additional QALY gained. For patients who fall into the low- and medium-risk groups, the incremental cost per QALY is $29,000 and $44,000, respectively (24). When comparing initiating dialysis and continuing aggressive care with with-
holding dialysis and providing comfort care, the incremental cost effectiveness of the aggressive treatment strategy is $310,000 for patients in the worst prognostic group (≤10% probability of surviving at least 6 months) but $71,000 for patients in the best prognostic group (>40% probability of surviving at least 6 months) (25).

Prior studies have examined the costs and outcomes associated with severe brain injury and the costs of life-sustaining treatments such as CPR. In a study of patients with traumatic coma, charges per favorable functional outcome (defined by the Glasgow Outcome Scale) were $1,540,971 for patients ≥60 yrs and $154,155 for patients aged 20 to 40 yrs (26). In a study of 515 patients with coma admitted to a French hospital between 1987 and 1993, the treatment costs varied widely and were associated with patient age, cause of coma, and severity of illness (27).

Researchers have evaluated cost savings associated with relatively early DNR orders and have documented the high costs associated with aggressive care, such as CPR. In a retrospective study of 852 patients who died in the hospital, published in 1993, average combined physician and hospital charges were $10,631 for patients who had a DNR order at admission and $73,055 for those who had a DNR order written during the hospitalization (28). In a review of the literature published in 1996, Lee et al. (29) reported that the patient’s underlying condition affected the cost effectiveness of CPR and estimated that the average cost of CPR programs was $406,605 per life saved and $225,892 per QALY saved. A study published in 1994 modeled the cost effectiveness of inpatient CPR and demonstrated that the cost per survivor increased exponentially as the rate of survival to discharge decreased ($117,000 for a rate of survival to hospital discharge of 10%, $248,271 for a rate of 1%, and $544,521 for a rate of 0.2%). Sensitivity analyses showed that stratifying hospitalized patients according to their prognosis and restricting use of CPR to those with better prognoses would substantially reduce healthcare costs (30).

Our study has several limitations. We focused on decision making by day 4 of coma because accurate prognostic estimates can be made using clinical information readily available by day 3. Whereas we focused on common and clinically relevant decisions faced by families and physicians, our cost-effectiveness analysis may oversimplify the complexity of real-life medical decisions. Decisions to use or withhold a wide variety of life-sustaining treatments occur throughout patients’ illnesses. We did not attempt to control for care decisions made later in patients’ hospitalizations; the data we used reflect the actual experiences of the patients in our study. Although a minority of the patients we studied had DNR orders written by day 4 of coma, the vast majority (86%) of patients who died within 2 months had DNR orders written before death. Our results, therefore, reflect a comparison between making earlier decisions to withhold life-sustaining treatments and not making or delaying such decisions.

We estimated healthcare costs incurred after the index hospitalization using Medicare data and assumed that costs for patients without Medicare insurance (i.e., most patients <65 yrs) were similar. In previous SUPPORT analyses, older age

Table 3. Baseline results and results of sensitivity analyses

<table>
<thead>
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<th>Low-Risk Patients</th>
<th>High-Risk Patients</th>
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<tr>
<td>Annual mortality after year 1</td>
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<td>200% of baseline estimate</td>
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<tr>
<td>Year 1 health care costs</td>
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<td>50% of baseline estimate</td>
<td>$77,000</td>
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QALY, quality-adjusted life year.
These limitations not withstanding, we found that continuing aggressive care after day 3 of nontraumatic coma (rather than restricting the use of life-sustaining treatments) for patients who have multiple risk factors for poor outcomes is associated with a very high incremental cost per quality-adjusted life year.

was (paradoxically) associated with lower costs (31); therefore, we may have slightly underestimated the costs for the full cohort, whose median age was 67 yrs. We had to project hospital costs after year 1 from cost data for the fourth quarter of year 1, but sensitivity analyses demonstrated that our conclusions were not sensitive to wide variations in estimates of these downstream costs. Patients were excluded from our study if they had coma caused by reversible metabolic abnormalities, and, therefore, our results are not generalizable to all patients with nontraumatic coma. Our estimates of survival, quality of life, and initial hospital costs were based on data from five medical centers; clinical outcomes and healthcare costs for patients treated at other settings, such as community hospitals, may differ. Finally, to the extent that medical care is withdrawn on the basis of poor prognosis, prognostic models can have a self-fulfilling prophecy effect.

These limitations not withstanding, we found that continuing aggressive care after day 3 of nontraumatic coma (rather than restricting the use of life-sustaining treatments) for patients who have multiple risk factors for poor outcomes is associated with a very high incremental cost per QALY. Our results suggest that making decisions in the first few days of coma to withhold life-sustaining treat-ments for patients with very poor prognoses may yield considerable cost savings.

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