Health state preferences and decision-making after malignant middle cerebral artery infarctions

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ABSTRACT

Objectives: Despite recent trials demonstrating improved functional outcomes in patients with malignant middle cerebral artery ischemic strokes treated with hemicraniectomy, survivors still experience significant stroke-related disability. The value assigned to health states with significant disability varies widely and may influence decisions regarding hemicraniectomy.

Methods: A medical decision analysis was used to evaluate the results of recent hemicraniectomy trials in terms of quality-adjusted life-years. Survival data and probability of various functional outcome states (modified Rankin score 2–3 or 4–5) at 1 year were abstracted from clinical trial data. Utility scores for modified Rankin states were abstracted from literature sources. Sensitivity analyses were performed to study results over a wide range of utility values. All modeling was performed on TreeAge Pro software.

Results: The hemicraniectomy treatment pathway was associated with more quality-adjusted life-years over the first year than the medical management pathway (0.414 vs 0.145). Hemicraniectomy remained the preferred option except when the utility associated with the possible outcome states dropped considerably (0.72 to 0.40 for Rankin 2–3, and 0.41 to 0.04 for Rankin 4–5), or when 1-week surgical mortality increased considerably (5% to 67%).

Conclusions: Over a 1-year time horizon, treating patients with malignant middle cerebral artery strokes with hemicraniectomy is associated with more quality-adjusted life-years than medical management alone, except under conditions where patients value possible resultant health states very poorly or surgical mortality is excessively high. *Neurology*® 2010;75:682–687

GLOSSARY

MCA = middle cerebral artery; **QALY** = quality-adjusted life-year; **QOL** = quality of life.

Large hemispheric infarctions with malignant edema, usually resulting from proximal occlusion of the middle cerebral artery (MCA) or the terminal internal carotid artery, are associated with significant morbidity and mortality, despite maximal medical management. Historical cohorts cite early mortality rates approximating 80%.¹

Hemicraniectomy has previously been described as a life-saving procedure with some improvement of functional outcomes, though much of these data were not from rigorously conducted clinical trials.² Recently published randomized clinical trials^{3–5} comparing early hemicraniectomy vs best medical management for malignant MCA infarctions, as well as a pooled analysis⁶ of these trials, have demonstrated better functional outcomes at 1 year in patients treated with hemicraniectomy.

Despite this, functional recovery following large MCA infarcts is incomplete. All patients in the recent pooled analysis had a modified Rankin scale score⁷ of at least 2, and the majority of surviving patients in the surgical group had scores of 3 or 4, representing significant disability.

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Figure 1 Decision model

mRS = modified Rankin Scale.

Assisting in a decision about hemicraniectomy includes teaching the family or surrogate decision-maker about the probability and types of possible health outcomes. Differences in how patients value living with significant stroke-related disability may affect the decision to pursue hemicraniectomy or other aggressive measures, vs opting for a more conservative (or even palliative) approach.

We created a decision model to evaluate the results of recent hemicraniectomy trials using quality-adjusted life-years (QALYs). We then used sensitivity analysis to determine whether varying the utility assigned to resultant modified Rankin scale scores could alter the decision to proceed with hemicraniectomy.

METHODS Decision modeling is an analytic tool designed to study complex decision-making with variable outcomes, specifically using quantitative techniques.⁸ This analysis adhered to principles of good practice regarding decision modeling for health care research purposes.⁹ We used QALYs as the outcome for this analysis; QALYs were calculated by assigning a value (utility) to a specific health state and multiplying this value by the amount of time (in years) spent in that health state.

All modeling was performed on TreeAge Pro software (Williamstown, MA). The decision tree is shown in figure 1. We used a static probability model to determine the amount of QALYs expected from treating patients with large MCA infarctions via a hemicraniectomy pathway or a medical management pathway.

Details of the hemicraniectomy procedure were provided in each of the 3 primary sources³⁻⁵ and were similar in description. Briefly, a flap involving portions of the temporal, frontal, parietal, and occasionally occipital bones was removed. An attempt

was made to remove as large an area as possible; generally, a diameter of >12 cm was preferred. Infarcted brain tissue was not resected. All other medical decisions (including mechanical ventilation and osmotherapy) in both treatment arms were left to the discretion of the treating physicians. This analysis used data from patients undergoing hemicraniectomy within 48 hours only.

A 1-year time horizon was used for this analysis, since reliable clinical trial data extending beyond 1 year were not available to input into the model. Decision nodes were created at 1 week, 30 days, 6 months, and 1 year, to represent the possibility of survival at each of these timepoints. These points were chosen based on their availability from literature sources.³ An additional decision node, representing the possibility of death during replacement of the bone flap, was added to the hemicraniectomy pathway after the 6-month node.

Probability data for survival at each decision node were abstracted from published sources.³ The probability of death during a flap replacement procedure was estimated by faculty members from the neurosurgery department at the University of Rochester Medical Center with significant vascular experience. These values are summarized in table 1.

Functional outcomes in patients surviving at 1 year were dichotomized into Rankin scores of 2–3 (moderate disability) or 4–5 (severe disability), and were abstracted from a pooled analysis⁵ included in the HAMLET publication. Utility values for these possible functional outcomes were obtained from a published review that included values determined from various methods and populations.¹⁰ The primary analysis was conducted using utility values obtained from stroke patients, in order to most accurately reflect the survivor experience. Utilities elicited through the time tradeoff methodology were chosen for the primary analysis since this method utilized the highest number of participants (973 subjects). Secondary analyses based on utilities elicited through other methods (visual analog scale, standard gamble) and from other populations (patients at risk for stroke, healthy adults) were also performed. A disutility value of 0.02 was deducted from hemicraniectomy patients who underwent

Table 1 Inputs into decision model

Variable description	Estimate	Range	Source
Probabilities			
1-week mortality (surgical)	0.05	0 to 1.0	3
30-day mortality (surgical)	0.2		3
6-month mortality (surgical)	0	0 to 1.0	3
1-year mortality (surgical)	0	0 to 1.0	3
Flap replacement mortality	0.001		^a
Rankin 2–3 at 1 year (surgical)	0.5		5
Rankin 4–5 at 1 year (surgical)	0.5		5
1-week mortality (conservative)	0.67		3
30-day mortality (conservative)	0.33		3
6-month mortality (conservative)	0	0 to 1.0	3
1-year mortality (conservative)	0	0 to 1.0	3
Rankin 2–3 at 1 year (conservative)	0.8		5
Rankin 4–5 at 1 year (conservative)	0.2		5
Utilities			
Death at 1 week (surgical)	0		^b
Death at 30 days (surgical)	0		^b
Death at 6 months (surgical)	0.14		^b
Death at 1 year (surgical)	0.41		^b
Death during flap replacement	0.29		^b
mRS 2–3 at 1 year (surgical)	0.7		^b
mRS 4–5 at 1 year (surgical)	0.39		^b
Death at 1 week (conservative)	0		^b
Death at 30 days (conservative)	0		^b
Death at 6 months (conservative)	0.14		^b
Death at 1 year (conservative)	0.43		^b
mRS 2–3 at 1 year (conservative)	0.72	0 to 1.0	10
mRS 4–5 at 1 year (conservative)	0.41	–0.2 to 0.8	10

Abbreviation: mRS = modified Rankin Scale.

^a Estimate from Neurosurgery Department at University of Rochester Medical Center.

^b Value was calculated or assumed as part of this study. See text for details.

flap replacement, to account for repeat hospitalization, pain, and other factors associated with this procedure.

A utility value of zero was assigned to patients who died at either the 7-day or 30-day timepoint. Patients who died between the 1-month and 6-month decision nodes were assumed to have died at approximately 3 months after their stroke; similarly, patients who died between the 6-month and 1-year decision nodes were assumed to have died at approximately 9 months after their stroke. The average of the 2 utilities used in the primary analysis (0.72 and 0.41, average 0.57) was then multiplied by the duration of time surviving (e.g., 0.25 years, 0.75 years) in order to calculate QALYs for these timepoints. All utility values are shown in table 1.

In one sensitivity analysis, the utility value for the Rankin 2–3 state was studied along the range from 0 to 1.0, and the utility value for the Rankin 4–5 state was studied along the range from –0.2 to 0.8, to account for health states valued worse than death. Specifically, we attempted to determine how poorly a patient or surrogate decision-maker would have to value a health state in order to influence the decision to proceed with hemicraniectomy.

We also performed a sensitivity analysis to determine what effect early surgical mortality (a possible indicator of surgical experience) would have on QALYs; this was done by varying the 1-week surgical mortality over the range from 0 to 1. A final sensitivity analysis was conducted in which 6-month and 1-year mortality was varied from 0 to 1 in both the medical and surgical groups, in order to account for the possibility that late mortality in clinical practice might differ substantially from that observed in the clinical trial setting.

RESULTS Using the inputs shown in table 1, treatment of a malignant MCA infarction via the hemicraniectomy pathway was associated with more QALYs than the medical management pathway. Specifically, hemicraniectomy was associated with 0.414 QALYs over the first year following stroke, compared with 0.145 QALYs resulting from the medical management pathway.

Treatment with hemicraniectomy was associated with an increased number of QALYs when utilities obtained from stroke survivors through other methodologies were analyzed (standard gamble method: 0.596 vs 0.189 QALYs; visual analog scale method: 0.255 vs 0.092 QALYs). Similarly, the benefit of hemicraniectomy was also observed when utilities elicited from patients at risk for stroke or healthy participants were substituted in the analysis (hemicraniectomy, QALYs ranging from 0.190 to 0.543; medical management, QALYs ranging from 0.089 to 0.184). These results are summarized in table 2.

The hemicraniectomy pathway remained the preferred option (i.e., associated with relatively more QALYs) except under conditions where the average utility value for the Rankin 2–3 outcome decreased from 0.72 to 0.40, and the average utility value for the Rankin 4–5 outcome decreased from 0.41 to 0.04. The results of this sensitivity analysis are shown graphically in figure 2.

When early surgical mortality was varied, the hemicraniectomy pathway remained associated with more QALYs than the medical pathway until 1-week surgical mortality increased to 67%. This is shown graphically in figure 3. Assuming no change in other conditional probabilities, the hemicraniectomy pathway was associated with more QALYs unless 6-month mortality in the hemicraniectomy pathway increased to 87% or higher and 6-month mortality in the medical pathway remained below 34%. The sensitivity analysis varying 1-year mortality revealed no conditions under which hemicraniectomy was not associated with more QALYs, even when 1-year mortality in the hemicraniectomy pathway was increased to 100%.

DISCUSSION Our study suggests that treatment of malignant MCA infarctions with hemicraniectomy is

Table 2 Expected outcomes for hemicraniectomy and medical management pathways using utility values from different sources/methods

Participants	Method ^a	Utility for mRS 2-3	Utility for mRS 4-5	Hemicraniectomy outcome (QALYs)	Medical management outcome (QALYs)
Stroke survivors	TTO	0.72	0.41	0.414	0.145
	SG	0.89	0.72	0.596	0.189
	VAS	0.46	0.25	0.255	0.092
At risk for stroke	TTO	0.55	0.26	0.293	0.109
	SG	0.81	0.45	0.463	0.163
	VAS	0.49	0.05	0.190	0.089
Healthy subjects	SG	0.90	0.57	0.543	0.184
	VAS	0.57	0.20	0.277	0.110
	EuroQOL	0.64	-0.04	0.213	0.111

Abbreviations: mRS = modified Rankin Scale; QALY = quality-adjusted life-year; QOL = quality of life; SG = standard gamble; TTO = time tradeoff; VAS = visual analog scale.

^a Method used to calculate utility.

associated with additional QALYs compared to medical management alone. The findings of this study are in keeping with the results of the pooled analysis and hemicraniectomy clinical trials, which showed a greater than 50% absolute decrease in mortality and a 16% absolute decrease in the rate of Rankin scores higher than 3 in patients treated with surgery. Our analysis extends these results through the use of a highly patient-centered outcome measure, which provides insights into the relative importance of quality of life (QOL) estimations in establishing patient-centered goals of care—estimations which may have life-and-death implications.

We found that if the decision-maker valued the resultant health state following severe stroke very poorly (less than 0.40 for Rankin 2-3 and less than 0.04 for Rankin 4-5), the QALYs gained with the medical management pathway were greater than with hemicraniectomy, despite having a lower sur-

vival. A utility value of 0 represents death, and provides a specific reference point in the decision-making discussion, specifically, “Would the patient consider this health state to be a fate worse than death?” If decision-makers feel confident that the patient would feel this way, then a conservative or palliative approach may be preferred.

The variation in how health states are defined and valued is of particular concern in patients with massive strokes, when surrogates are often making treatment decisions. Prior research has demonstrated that participants who are naïve to a clinical condition often underestimate the QOL associated with that state.¹¹ Specifically regarding this study population, previous data have noted that surrogates tend to rate patients as more impaired and having lower QOL than the patients themselves, and that this discordance between patient and surrogate opinion was more pronounced in situations with severe deficits.¹² If this type of estimation error occurs in clinical practice, the potential exists to underuse hemicraniectomy. By using utility values obtained from a variety of sources (including stroke survivors and healthy subjects) and performing a sensitivity analysis with a wide range of utility scores, we attempted to address this possibility, and found that only with gross underestimation was hemicraniectomy not the preferred option.

Beyond inappropriately estimating the value patients may place on certain health states, there are also concerns about how accurately surrogates reflect patient decisions after stroke. In a systematic review of surrogate decision-maker performance, it was shown that surrogates predicted patient treatment preferences with only 68% accuracy; surrogate performance was worst regarding stroke-related scenarios, where accuracy was 58%.¹³ Many of these scenarios involved intervention decisions regarding intubation/mechanical ventilation, artificial hydration/nutrition, and surgical procedures, precisely the types of interventions that are often necessary following large MCA infarctions. Further research is needed to better understand why surrogate decisions are frequently in conflict with those of patients, particularly in the area of stroke.

In addition to those of surrogates, opinions and actions of health care providers may lead to potential overutilization or underutilization of hemicraniectomy and other life-sustaining measures. Possibilities include erroneous or biased estimations of future outcomes, misinterpretation of patient and family values, and conscious or subconscious communication of outcomes in a particular optimistic or pessimistic light.¹⁴ Some of these factors (particularly regarding biases and subconscious messages) may

Figure 2 Sensitivity analysis performed by varying utility values for modified Rankin Scale score (mRS) 2-3 and 4-5

Gray area = hemicraniectomy; green hatch area = medical management.

Figure 3 Sensitivity analysis performed by varying early (1-week) surgical mortality

QALY = quality-adjusted life-year.

be minimized through the use of formal patient decision aids, which have been shown in select circumstances to improve the quality of decisions and decrease interventions that patients may not value.¹⁵ Decision aids have been infrequently studied in stroke, but represent a possible area of future research.

Our sensitivity analysis on early surgical mortality suggests that this rate must be considerably higher than the mortality rate observed in clinical trials before hemicraniectomy is not associated with more QALYs than medical management. This magnitude of difference is important, since the efficacy of surgery seen in a clinical trial setting may be greater than the effectiveness seen in routine clinical practice. These results highlight that early surgical care (and mortality), unless drastically different from that seen in the trial setting, is unlikely to alter the patient outcome.

The design of our decision model has some limitations that may have underestimated the effects of hemicraniectomy. First, we used a 1-year time horizon based on the availability of high-level clinical data over this time frame. By extending the time horizon, we would expect the mortality benefit seen in hemicraniectomy patients to continue to persist. In addition, the distribution of Rankin scores might continue to improve, as patients hopefully continue to receive appropriate rehabilitation services and adapt to their stroke-related deficits.

Second, we chose to dichotomize the functional outcomes into Rankin scores of 2–3 and 4–5. This paradigm has previously been described¹⁶ to help practically delineate patients with no or mild deficits (Rankin 0–1), moderate deficits (Rankin 2–3), or severe deficits (Rankin 4–5). Further, specific utility values and ranges were not readily available for each

individual Rankin score. In the first pooled analysis,⁶ the hemicraniectomy group had a higher proportion of patients with Rankin scores of 2 and 4 (the better outcomes within our grouped categories of Rankin 2–3 and 4–5) as compared to the conservative management group; as a result, using individual Rankin scores may have further favored hemicraniectomy.

In our analysis, we converted functional outcomes as measured by the Rankin scale to a more quantitative utility value. An alternative would be to use QOL assessments from survivors of malignant infarctions, including those having undergone hemicraniectomy. However, data in this area are largely restricted to case series^{17–22} with variable follow-up times, and investigate only hemicraniectomy patients, thereby eliminating an effective comparison group. Furthermore, some studies reported right hemispheric infarcts alone^{18,20} and most data involved patients undergoing surgery beyond 48 hours; thus, the applicability to this analysis and current practice is uncertain. Available QOL data suggest that motor function is typically more impaired than psychosocial domains, and that in general, patients and caregivers would retrospectively have consented to surgery again (rates varying from 50%¹⁷ to 100%⁵).

We chose to use conditional probabilities of mortality from the DECIMAL³ trial in our model, since this study provided interval data at numerous early timepoints as well as a survival curve extending to beyond 1 year. While these conditional probabilities were drawn from a relatively small number of participants, our sensitivity analyses regarding early, 6-month, and 12-month mortality studied these conditional probabilities across a wide range, hopefully mitigating some of the uncertainty around these estimates.

The same inclusion and exclusion criteria (e.g., age 18–60 years) that somewhat limit the applicability of the hemicraniectomy trial data also apply to our results. Specifically, applying these results to older patients with multiple comorbid conditions in whom stroke survival and recovery may be diminished should be done with caution. Further, our findings do not directly account for patients who have clearly documented advance directives regarding their care; these obviously need to be a critical part of the decision-making process. Finally, it should be noted that these results are potentially limited to patients undergoing a hemicraniectomy procedure within 48 hours of stroke onset, based on the findings of DECIMAL,³ DESTINY,⁴ the pooled analysis,⁶ and a subset of the HAMLET⁵ trial. A separate aim of the HAMLET trial investigated the role

of hemicraniectomy out to 96 hours and did not find a benefit.

The number of patients undergoing hemicraniectomy is likely to increase given the recent clinical trial results. With this increased number of survivors, we should strive for better understanding of patient-specific outcomes, including long-term QOL measurements, which can then be incorporated into the early decision-making process. Physicians and other health providers must become highly effective at communicating all possible alternatives, their potential range of outcomes, and the expected morbidity/QOL associated with each. Finally, the identification and counseling of surrogate decision-makers for patients at risk for stroke is of crucial importance, since inaccurate estimation of health-related QOL can mean the difference between life and death.

DISCLOSURE

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