ORIGINAL ARTICLE

A Randomized Trial of Enteral Glutamine for Treatment of Burn Injuries

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ABSTRACT

BACKGROUND

Glutamine is thought to have beneficial effects on the metabolic and stress response to severe injury. Clinical trials involving patients with burns and other critically ill patients have shown conflicting results regarding the benefits and risks of glutamine supplementation.

METHODS

In a double-blind, randomized, placebo-controlled trial, we assigned patients with deep second- or third-degree burns (affecting ≥10% to ≥20% of total body-surface area, depending on age) within 72 hours after hospital admission to receive 0.5 g per kilogram of body weight per day of enterally delivered glutamine or placebo. Trial agents were given every 4 hours through a feeding tube or three or four times a day by mouth until 7 days after the last skin grafting procedure, discharge from the acute care unit, or 3 months after admission, whichever came first. The primary outcome was the time to discharge alive from the hospital, with data censored at 90 days. We calculated subdistribution hazard ratios for discharge alive, which took into account death as a competing risk.

RESULTS

A total of 1209 patients with severe burns (mean burn size, 33% of total body-surface area) underwent randomization, and 1200 were included in the analysis (596 patients in the glutamine group and 604 in the placebo group). The median time to discharge alive from the hospital was 40 days (interquartile range, 24 to 87) in the glutamine group and 38 days (interquartile range, 22 to 75) in the placebo group (subdistribution hazard ratio for discharge alive, 0.91; 95% confidence interval [CI], 0.80 to 1.04; P=0.17). Mortality at 6 months was 17.2% in the glutamine group and 16.2% in the placebo group (hazard ratio for death, 1.06; 95% CI, 0.80 to 1.41). No substantial between-group differences in serious adverse events were observed.

CONCLUSIONS

In patients with severe burns, supplemental glutamine did not reduce the time to discharge alive from the hospital. (Funded by the U.S. Department of Defense and the Canadian Institutes of Health Research; RE-ENERGIZE ClinicalTrials.gov number, NCT00985205.)

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Worldwide, burn injuries are the leading cause of disability-adjusted life-years lost in low- and middle-income countries and among the most expensive to treat of traumatic injuries.[1-3] The intense inflammation and catabolism associated with severe burns predispose patients to an increased risk of infectious complications, short- and long-term organ dysfunction, and death.[4]

Numerous trials have evaluated the effect of different nutritional strategies in patients with severe burns.[5,6] Glutamine is of particular interest because it is vital for a number of key stress-response pathways in serious illness.[7] Observational studies have shown that glutamine levels decrease rapidly after burn injury.[8-10] In critically ill patients, low levels of glutamine are associated with increased morbidity and mortality.[11-14] Several small, single-center, randomized, controlled trials, when statistically aggregated, suggest a dramatic reduction in mortality and length of hospital stay associated with enteral glutamine supplementation in patients with burns.[15] International nutrition guidelines for major burns include a recommendation for enteral glutamine.[6] A survey of 37 burn units worldwide showed that 47.7% of mechanically ventilated patients with burns received glutamine supplementation.[16] However, randomized, controlled trials involving other critically ill patient populations have suggested that glutamine administration may be ineffective or even harmful.[17,18] Given these conflicting data, a higher level of evidence was needed to inform clinical recommendations regarding the use of glutamine in this unique population.

We conducted an international, double-blind, parallel-group, randomized, placebo-controlled trial to evaluate the effect of supplemental enteral glutamine on the time to discharge alive in patients with severe burn injuries.[19] The aim of the trial was to determine whether this inexpensive therapeutic strategy leads to lower morbidity and mortality or whether it should be abandoned.

METHODS

TRIAL DESIGN AND PATIENTS

The Randomized Trial of Enteral Glutamine to Minimize the Effects of Burn Injury (RE-ENERGIZE) protocol has been published previously[18] and is available with the full text of this article at NEJM.org. This investigator-initiated trial was designed by the first author (the principal investigator) and the last author (the trial statistician), in consultation with the steering committee. Collectively, the steering committee vouches for the completeness and accuracy of the data, the adherence of the trial to the protocol, and the decision to submit the manuscript for publication. All sites and personnel that participated in the data collection are listed in the Supplementary Appendix (available at NEJM.org), and confidentiality agreements were in place with all participating sites. The last author supervised Xuran Jiang, a data analyst at Queen's University who conducted the analysis. The first author and the writing committee wrote the manuscript. The trial protocol was approved by the research ethics committees at Queen's University and all participating centers. The trial agents were provided by Emmaus. The entities that provided financial and product support for the trial had no role in designing the protocol, conducting the trial, or analyzing the data and did not have access to the data or the manuscript before publication. Written informed consent was obtained from each patient or the patient's designated surrogate before randomization.

We enrolled adult patients presenting to participating hospitals who had second- or third-degree burns and who were expected to require skin grafting. The threshold burn size that we used to define a major burn varied according to the patient's age: patients 18 to 39 years of age with a burn affecting 20% or more of total body-surface area, or 15% or more when concomitant inhalation injury was present; patients 40 to 59 years of age with a burn affecting 15% or more of total body-surface area; and patients 60 years of age or older with a burn affecting 10% or more of total body-surface area. We excluded patients if they had not provided consent within 72 hours after admission to the acute care unit (either an intensive care unit or a burn unit), were in a moribund state, or had a contraindication to enteral nutrition. Minor changes to the eligibility criteria were made during the duration of the trial; see the Supplementary Appendix for details of changes and a complete list of exclusion criteria.

RANDOMIZATION AND BLINDING

Randomization was stratified according to site in permuted blocks of random size (2, 4, or 6). After informed consent was obtained, eligible patients were randomly assigned (in a 1:1 ratio) to receive either enteral glutamine or placebo. Randomization was performed with the use of a central Web-based randomization system. The local pharmacist, who was aware of the trial-group assignments, dispensed the appropriate blinded trial agent.

TRIAL AGENTS

In the glutamine group, patients received glutamine every 4 hours through a feeding tube or three or four times a day by mouth if they were not using a feeding tube, for a total of 0.5 g per kilogram of pre-burn body weight per day. However, for patients with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 35 or more, an obesity-adjusted body weight was used. The glutamine powder was supplied in prepackaged aliquots and was delivered to the acute care unit in blinded sachets and was mixed in water or other liquids or food at the bedside by the patient's nurse.

In the placebo group, patients received an isocalorically delivered amount of maltodextrin (control) mixed with water or other liquids or food. We chose a non-isonitrogenous placebo because both trial groups received adequate protein through standard nutritional care. In addition, nonessential amino acids used in such a placebo may have active metabolic and cellular effects, and their use could also compromise blinding of the trial owing to the differences in appearance. The trial agents were given until 7 days after the last skin grafting procedure, discharge from the acute care unit, or 3 months after admission, whichever came first.

Nutrition practices were reviewed at each site to standardize the administration of macro- and micronutrients, and nutrition-related data were collected for mechanically ventilated patients. All other burn care was left to the discretion of participating sites.

OUTCOMES, TRIAL MODIFICATION, AND RATIONALE FOR SAMPLE SIZE

The original primary outcome for this trial was 6-month mortality, and the secondary outcome was the time to discharge alive from the hospital. We initially planned to enroll 2700 patients to achieve 80% power at an overall two-sided alpha level of 0.05 to detect a 25% relative reduction in mortality from 15% to 11.5%, allowing for two interim analyses and 5% loss to follow-up. However, after 4 years of enrollment and 690 patients had been enrolled at 41 sites, it became clear that the original sample size was not feasible, so we switched the primary and secondary outcomes. Using the existing blinded data set at that time to confirm pooled event rates, we estimated that if the glutamine group had a 20% relative reduction in 90-day mortality (from 15.56% to 12.44%) and a 20% relative increase in the daily rate of discharge among 90-day survivors, then a sample size of 1200 would achieve 80% power to detect a difference in the time to discharge alive at a two-sided alpha level of 0.05 (details are provided in the statistical analysis plan, available with the protocol). The time to discharge alive has the advantage of combining the effect on survival and any benefit from an earlier discharge from the hospital, which may be mediated by the positive effects of glutamine on infection, wound healing, and organ function. One interim analysis was performed after 600 patients had been enrolled. This analysis would have led to a recommendation to stop the trial if mortality was greater in the glutamine group at a one-sided alpha level of 0.01.

Data on tertiary hospital outcomes were censored at 90 days. These included the incidence of acquired bacteremia due to gram-negative organisms, in-hospital mortality, the duration of mechanical ventilation, length of stay in the acute care unit, and length of stay in the hospital. At 6 months, the local research coordinator contacted patients by telephone to administer the 36-item Short Form Health Survey (scores for each domain range from 0 to 100, and the physical and mental component summaries are defined to have a mean of 50 and standard deviation of 10 in the general U.S. population; higher values indicate better health-related quality of life), the Katz Index of Independence of Activities of Daily Living (scores ranges from 0 to 6, with higher scores indicating a higher level of independence), and the Lawton Index of Instrumental Activities of Daily Living (scores

range from 0 to 8, with higher scores indicating better functioning).[20-22]

STATISTICAL ANALYSIS

The primary outcome, the time to discharge alive, was compared between trial groups with the use of the cumulative-incidence function and corresponding Gray's test for competing risks.[23] Secondary analyses that were stratified according to site or that included site as a random effect were run with the use of a proportional-hazards model to estimate the subdistribution hazard ratio (which takes into account death as a competing risk) and the corresponding Fine and Gray's test.[24,25] The model was repeated with the addition of the following prespecified baseline covariates: age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, baseline Sequential Organ Failure Assessment (SOFA) score, burn size as a percentage of total body-surface area, Charlson comorbidity index score, and geographic region. The aforementioned analyses treated death as a competing risk precluding discharge and censored data from patients at the earlier of 90 days or (rarely) the time of withdrawal of consent. Patients who died within 72 hours after hospital discharge were categorized as decedents who were not discharged alive. Mortality by 6 months was estimated with the use of the Kaplan–Meier method, with data censored at the last date that the patient was known to be alive up to 6 months after randomization. The difference between trial groups in 6-month survival was assessed by means of hazard ratios estimated with the use of a Cox proportional-hazards model.

In prespecified subgroup analyses, we examined the treatment effect of glutamine across age, burn size as a percentage of total body-surface area, and age plus burn size as a percentage of total body-surface area for the primary and secondary outcomes. Details are provided in the Supplementary Appendix.

The modified intention-to-treat analysis, performed with the use of SAS software, version 9.4 (SAS Institute), included all randomly assigned patients in the group to which they were assigned unless they left the trial early before receiving glutamine or placebo. Confidence intervals were not adjusted for multiplicity, so inferences drawn from secondary and tertiary outcomes may not be reproducible. Further details, including the description of the analysis of tertiary outcomes, are provided in the Supplementary Appendix and the statistical analysis plan.

Figure 1 (facing page). Screening, Randomization, and Follow-up.

A patient could meet more than one exclusion criterion or have more than one reason for not giving consent. For time to discharge from the hospital or death, data were censored if patients remained in the hospital at 90 days. For the primary time-to-event analysis, data from patients lost to follow-up owing to withdrawal of consent were censored at the time of withdrawal of consent, so all 1200 patients who received glutamine or placebo were included in the analysis. ADL denotes activities of daily living, BMI body-mass index, and SF-36 the 36-item Short Form Health Survey.

RESULTS

PATIENT CHARACTERISTICS

From May 2011 through June 2021, we enrolled 1209 patients at 54 burns units in 14 countries (Fig. 1). A total of 9 patients died, withdrew consent, or were discharged before receiving the first dose of glutamine or placebo, which resulted in an intention-to-treat population of 1200 patients, of whom 596 were assigned to the glutamine group and 604 were assigned to the placebo group. Data on the primary outcome were available for the entire intention-to-treat population. The trial groups had similar characteristics at baseline (Table 1). The representativeness of the sample is described in Table S1 in the Supplementary Appendix.

ADHERENCE TO THE PROTOCOL AND TRIAL AGENTS

The treatment period lasted for a mean of 26 days overall. Adherence to the protocol was high, and protocol deviations were similar in the two groups; 91% of the doses of each trial agent were delivered. The time to first excision and débridement was 3 to 4 days after hospital admission; no substantial differences between groups were observed. Mechanically ventilated patients received approximately 73% of their prescribed protein and energy requirements (Table S2).

PRIMARY OUTCOME

We found no evidence of a significant difference in the time to discharge alive between the trial groups (Fig. 2). The cumulative incidence of discharge alive and its competing risk of death are

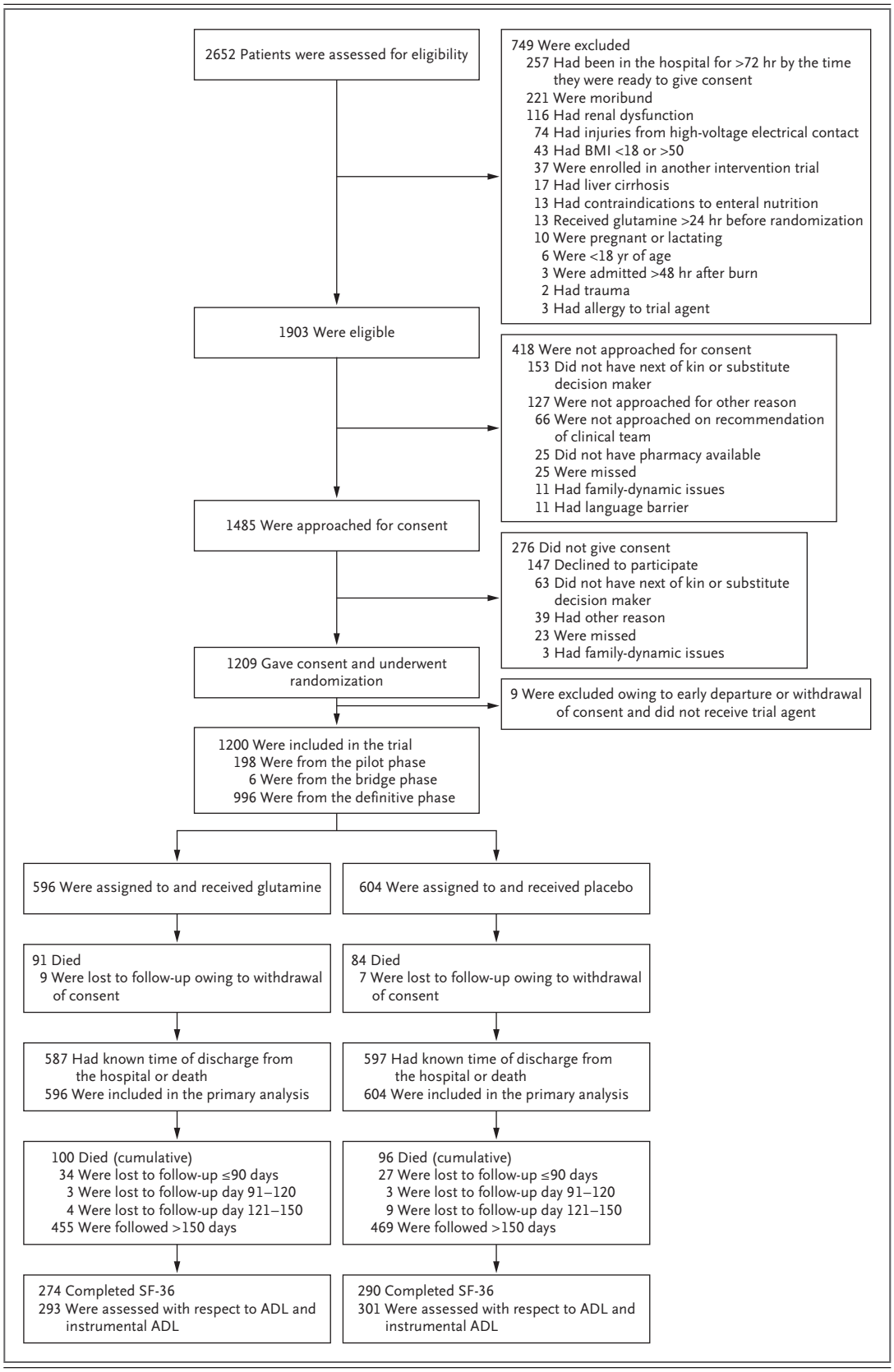


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Glutamine (N = 596)	Placebo (N = 604)
Age — yr		
Mean	49.7±18.1	49.1±17.8
Range	18.0–93.0	18.0–91.0
Sex — no. (%)		
Male	431 (72.3)	457 (75.7)
Female	165 (27.7)	147 (24.3)
Race or ethnic group — no. (%)†		
White	453 (76.0)	455 (75.3)
Black	44 (7.4)	53 (8.8)
Hispanic	42 (7.0)	53 (8.8)
Asian or Pacific Islander	27 (4.5)	25 (4.1)
First Nations	21 (3.5)	10 (1.7)
East Indian	4 (0.7)	0
Other	5 (0.8)	8 (1.3)
Tobacco use at time of admission — no. (%)		
Yes	197 (33.1)	190 (31.5)
No	267 (44.8)	273 (45.2)
Not available	132 (22.1)	141 (23.3)
APACHE II score‡		
Mean	14.2±8.2	14.1±7.9
Range	1.0–45.0	1.0–46.0
Charlson comorbidity index score§		
Mean	0.5±1.2	0.4±0.9
Range	0.0–13.0	0.0–7.0
Burn size — % of total body-surface area		
Mean	33.1±17.4	31.9±15.6
Range	10.0–93.0	10.0–85.0
Type of burn — no. (%)		
Scald	41 (6.9)	41 (6.8)
Fire	525 (88.1)	541 (89.6)
Chemical	18 (3.0)	11 (1.8)
Other	12 (2.0)	11 (1.8)
Body-mass index		
Mean	28.2±5.9	28.1±5.8
Range	17.0–49.7	18.0–49.4
Modified SOFA score¶		
Mean	3.1±2.9	3.2±3.0
Range	0.0–13.0	0.0–14.0
Hours from burn injury to initiation of trial agent		
Mean	60.8±32.2	59.5±26.8
Median (IQR)	61.0 (41.0–74.6)	59.5 (40.6–73.5)
Range	8.0–493.0	6.6–209.0

Table 1. (Continued.)

Characteristic	Glutamine (N=596)	Placebo (N=604)
Coenrolled in another academic study — no./total no. (%)‖	45/492 (9.1)	52/504 (10.3)
High-dose vitamin C as part of resuscitation protocol — no./total no. (%)‖	24/492 (4.9)	21/504 (4.2)
Receipt of mechanical ventilation at time of randomization — no. (%)	242 (40.6)	239 (39.6)
Geographic region — no. (%)		
United States	338 (56.7)	337 (55.8)
Canada	100 (16.8)	102 (16.9)
Europe, not including the United Kingdom	73 (12.2)	73 (12.1)
United Kingdom	48 (8.1)	55 (9.1)
Latin America	23 (3.9)	25 (4.1)
Asia	14 (2.3)	12 (2.0)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race and ethnic group were reported by the patient or the patient's designated surrogate. Examples of "First Nations" are Native American and Canadian Inuit.
‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating greater disease severity and a higher risk of death. Data were not available for two patients in the glutamine group and four patients in the placebo group.
§ Scores on the Charlson comorbidity index range from 0 to 40, with higher scores indicating a greater burden of coexisting conditions.
¶ Scores on the Modified Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating more severe disease.
‖ Data for this characteristic were available only for the definitive phase of the trial.

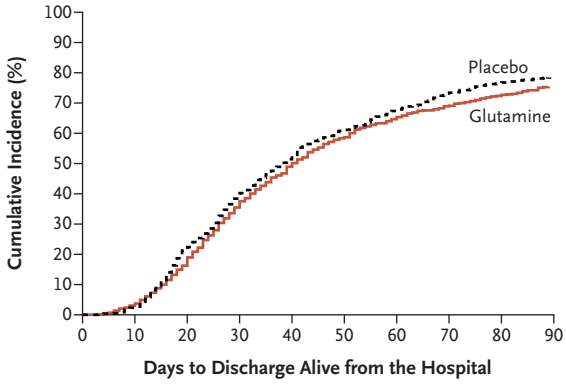
depicted in Figure S1. The median time to discharge alive from the hospital was 40 days in the glutamine group and 38 days in the placebo group (subdistribution hazard ratio for discharge alive, 0.91; 95% confidence interval [CI], 0.80 to 1.04; P=0.17). Results did not differ when adjusted according to site or important covariates (Table 2), and the subgroup analyses showed no suggestion of subgroup effect (Fig. S2).

SECONDARY OUTCOME

The 6-month mortality was 17.2% in the glutamine group and 16.2% in the placebo group (hazard ratio for death, 1.06; 95% CI, 0.80 to 1.41) (Fig. S3). The subgroup analyses showed no suggestion of subgroup effect (Fig. S4).

TERTIARY OUTCOMES

In-hospital mortality, length-of-stay variables, and the incidence of bacteremia due to gram-negative organisms were similar in the two groups (Table 3). At 6-month outcome assessments, we found no evidence of clinically significant be-



No. of Patients			
Placebo			
In hospital	297	114	44
Deceased	59	77	84
Glutamine			
In hospital	308	122	52
Deceased	59	83	91

Figure 2. Time to Discharge Alive from the Hospital, According to Trial Group.
This figure shows the cumulative incidence of discharge alive from the hospital (primary outcome), assessed in a time-to-event analysis.

Table 2. Time to Discharge Alive from the Hospital.

Analysis	Glutamine (N=596)	Placebo (N=604)	Subdistribution Hazard Ratio (95% CI)*	P Value
Primary analysis: median no. of days to discharge alive from the hospital (IQR)	40 (24–87)	38 (22–75)	0.91 (0.80–1.04)†	0.17
Secondary analysis stratified according to site			0.89 (0.78–1.02)	0.08
Secondary analysis with site as a random effect			0.88 (0.77–1.00)	0.06
Secondary analysis with site as a random effect and with adjustment for age, APACHE II score, baseline SOFA score, burn size, Charlson comorbidity index score, and geographic region			0.92 (0.81–1.05)	0.22

* Subdistribution hazard ratios for discharge alive take into account death as a competing risk. Hazard ratios of less than 1 favor placebo.
† This hazard ratio is unadjusted.

tween-group differences in health-related quality-of-life scores, activities of daily living, or instrumental activities of daily living (Tables S3 and S4).

SAFETY ASSESSMENTS

We observed small increases in urea levels in patients who received glutamine, but no substantial difference in the incidence of acute kidney injury or use of renal-replacement therapy as compared with patients who received placebo (Table S5). Serious adverse events were similar in the two groups (Table S6).

DISCUSSION

In this international, multicenter, randomized, controlled trial involving adults with major burns, the time to discharge alive from the hospital was not shorter among patients who received enteral glutamine than among those who received placebo. We did not find any evidence to suggest between-group differences in 6-month mortality, length-of-stay variables, or the incidence of bacteremia.

Our results were unexpected given the magnitude of the signal from previous trials of supplemental glutamine in burn-injured patients.[15] Our trial differed from the previous trials in several important ways. First, the previous randomized, controlled trials were small, single-center trials ranging from 30 to 48 patients each. Our multicenter trial with a much larger sample showed no combined effect of reduced mortality and shorter hospital stay (the 95% confidence interval for the subdistribution hazard ratio for discharge alive [0.80 to 1.04] ruled out a clinically meaning benefit). Previous research has shown that the effect of intravenous glutamine was also subject to a single-center bias in which all the positive effects were seen in single-center, randomized, controlled trials, whereas larger, multicenter, randomized, controlled trials did not confirm a positive treatment effect.[26] Others have shown how the results of single-center trials consistently overestimate the treatment effect as compared with larger multicenter trials.[27] The practice of translating the results of single-center trials into clinical-practice recommendations, as occurred with enteral glutamine supplementation, should be reexamined.

Second, the management of burn injury has evolved in the past decade since the publication of results of previous trials (from 2003 through 2009), and in most geographic areas worldwide, there has been a substantial decline in the mortality and morbidity associated with burn injury.[28] With greater attention to initial resuscitation, wound management, and early surgical intervention, it may be unlikely that a single-nutrient replacement strategy will affect the underlying pathophysiological processes.

The strengths of this trial include its robust scientific methods and high-fidelity implementation, which enhance the internal validity of the findings. The large number of diverse patients recruited across a large global network of burn units supports broad generalizability of the findings.

The major weakness of this trial is the low

Table 3. Tertiary Hospital Outcomes.

Outcome	Glutamine (N=596)	Placebo (N=604)	Treatment Effect (95% CI)*	
			Unadjusted	Adjusted†
Death in the hospital — no. (%)	91 (15.3)	84 (13.9)	1.10 (0.83 to 1.44)‡	0.96 (0.79 to 1.16)‡
Incidence of acquired bacteremia due to gram-negative organisms — no. (%)	113 (19.0)	109 (18.0)	1.05 (0.83 to 1.33)‡	0.97 (0.80 to 1.16)‡
Days in the hospital§				
No. of patients evaluated	587	597		
Median no. of days (IQR)	32.0 (20.0 to 53.0)	30.0 (18.0 to 53.0)	1.61 (–1.20 to 4.42)¶	0.92 (–1.57 to 3.41)¶
Days to live discharge from acute care unit‖**				
No. of patients evaluated	596	604		
Median no. of days (IQR)	36.0 (21.0 to 81.5)	35.0 (19.0 to 67.0)	0.90 (0.80 to 1.03)††	0.91 (0.79 to 1.03)††
Days to live extubation from mechanical ventilation**				
No. of patients evaluated	340	351		
Median no. of days (IQR)	17.0 (7.0–29.0)	15.0 (6.0–28.0)	0.91 (0.77 to 1.07)††	0.91 (0.77 to 1.08)††

* Confidence intervals were not adjusted for multiplicity of outcomes, so inferences drawn may not be reproducible, and all intervals include an estimate of no difference between groups.
† Values were controlled for random site effect and fixed effects for age, APACHE II score, baseline SOFA score, burn size as a percentage of total body-surface area, Charlson comorbidity index score, and geographic region.
‡ Shown is the relative risk. Values of less than 1 favor glutamine.
§ Data for days in the hospital exclude patients who withdrew consent for further data collection while in the hospital and truncate hospital duration at 90 days.
¶ Shown is the mean difference.
‖ Acute care units include burn units and intensive care units.
** Death was a competing event precluding discharge or extubation.
†† Shown is the hazard ratio. Values of less than 1 favor placebo.

accrual that led to the alteration of the sample size and primary outcome. Although blinded sample-size reestimation is widely accepted to have only trivial effects on type I error, we cannot rule out the possibility that the midtrial alterations could slightly distort the type I and II error rates.[29,30] An additional weakness is the low completion rate of 6-month survivor questionnaires, albeit the rate was similar to or higher than those in other burn-care studies of this nature. Finally, the trial statistician (who is on the steering committee) conducted the interim analysis, but this analysis included only baseline characteristics, adverse events, and deaths, and results were kept from the rest of the steering committee to avoid influence on decisions regarding trial changes.

In this trial involving patients with severe burns, supplemental enteral glutamine did not reduce the time to discharge alive from the hospital.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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