NET FLUID ACCUMULATION AND OUTCOME. A RANDOMIZED CLINICAL TRIAL

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SUMMARY. Outcome measures are the first step in determining the consequences of health care. These include mortality, morbidity, and quality of life. As major burns are life-threatening conditions, the main priority in discussing outcome measures is mortality as a problem-specific measure. A number of studies have shown that mortality is predominantly determined by many variables obtained as “admission” predictors” as also by numerous variables obtained during the hospital course. Net fluid accumulation (NFA) is one of the many important factors that correlate with clinical outcome. The purpose of this paper is thus to evaluate NFA during resuscitation with Ringer’s lactate (RL) and its relationship with mortality. We hypothesized that rigorous monitoring of fluid replacement therapy might result in lower fluid retention, which could be effective in the prognosis of severely burned patients. In this prospective randomized study, the patients were divided into two groups of 55 cases each. In RL group 1, the patients were resuscitated using the Parkland formula in adults and the Galveston Shriner formula in children, without modifications, while in RL group 2 the formula was utilized as a starting-point only and the amount of fluid was modified in each case on the basis of the clinical situation and urine output. It was found that there was a statistically significant difference in NFA between the two groups (p = 0.001), as also a statistically significant difference between the amount of fluids given and the complications (p = 0.08). The majority of patients who died (70%) presented higher NFA values in the period of resuscitation. There was a statistically significant difference between mortality and total body surface area burned (p = 0.036), co-morbidities (p = 0.015), cause of burn (p = 0.004), inhalation injury (p = 0.027). The degree of NFA correlated, with a linear positive relationship, with morbidity (Kendall’s tau_br = 0.143, p = 0.019) and, with a negative relationship, with mortality (Kendall’s tau_br = 0.234, p = 0.001). Mortality as the primary endpoint was 16% in group 1 and 9% in group 2. Giving the smallest amount of fluids necessary for adequate resuscitation can be effective in creating a successful and specific therapy for all burn patients. With regard to morbidity and mortality, predictor factors, as also the method of resuscitation, have an influence in maintaining constant NFA values.

Introduction

Health care systems struggle with ways to provide higher quality care. Outcome measures are the first step in determining the consequence of health care. As major burns are life-threatening, the main priority is the preservation of life. Outcome measures include mortality and morbidity in the intermediate term, and quality of life and exercise tolerance, which are the two important long-term outcome measures.

In major burns, the choice of outcome measures is mortality as a problem-specific measure. When we treat severe burns, the problem we have to study may lead to premature death, and a reduction in mortality is a meaningful endpoint. Traditionally, demographic and injury variables such as age, gender, burn extent, and the presence of inhalation injury have been used to predict mortality after severe burns. Many scoring systems - the Baux Index, the Abbreviated Burn Severity Index, the Unit Burn Standard, and others - have been reported as predicting mortality. The principle feature of these scoring systems is that they use demographic and injury variables obtained at admission.

Many studies have shown that mortality appears to be predominantly determined by variables obtained during the hospital course. These factors include the time required to establish venous access, early and adequate resuscitation, early excision, and grafting, amelioration of the hypermetabolic response, and the development of sepsis and organ failure and ventilator dependency. Some clinical studies have shown that persistent hyperglycaemia and a sustained increased acute phase response can be potentially life-threatening, contributing to multiple organ failure complications and death.

Net fluid accumulation (NFA) is the difference between cumulative fluids and cumulative urine output. Expressed in ml/kg, it is an important parameter for monitoring the fluid balance. According to Geir, the degree of fluid accumulation correlates with the gravity of the thermal injury and the clinical outcome. Carlson showed that net fluid retention was a better predictor of mortality than burn area, age, sex, and the presence or absence of inhalation injury in burn-injured patients.

We present this clinical study in order to evaluate NFA
Our main research objective was to evaluate the effect of NFA on overall mortality.

**Method**

This is a prospective clinical and analytical study. 

*Eligibility criteria.* The study included patients with severe burns hospitalized in an intensive care unit within the first 24 h post-burn. The patients were of all age groups (children, adults, and the elderly), with or without inhalation injury and coexisting morbidities. The patients were not admitted to the study if any of the following criteria were present: patients admitted to hospital 24 h post-burn, pathologies other than burns.

*Setting and location.* The study was carried out in the Burns Service of the Mother Teresa University Hospital Centre in Tirana, Albania. The patients were from Tirana and the rest of the country.

*Interventions in each group of patients.* The patients were divided into two groups of 55 cases each. In Ringer’s lactate (RL) group 1 patients were resuscitated with the Parkland formula in adults and the Galveston Shriners formula in children without modifications, while in RL group 2 the formulas were utilized as a starting point only, after which the amount of fluid was modified according to the clinical situation and urine output.

All data were recorded on a special chart. Fluid therapy in the first 24 h was monitored, taking into consideration urine output, heart rate, and arterial blood pressure, and complete blood tests were performed every 4 h, including haematocrit and haemoglobin, plasma sodium, and plasma and urine osmolality. In particular we recorded NFA at every hour of resuscitation.

*Specific objectives.* In this study we aimed to be rigorous in the monitoring of the fluid replacement therapy, resulting in specific treatment for each patient. Specific objectives included fluid loads (ml/kg/% BSA), sodium loads (mEq/kg/% BSA), NFA (ml/kg), and sodium balance.

*Primary and secondary outcome measurements.* The primary endpoint of outcome is mortality. We provide data about overall mortality at the end of the disease and the relationship between NFA and mortality. The development of the systemic inflammatory response syndrome (SIRS)/sepsis constitutes a secondary clinical outcome.

*Sample size.* In order to determine sample size, we took into consideration: \( \alpha = 0.05 \) (two sided), statistical power = 0.8 or 80%, groups with equal number of patients, and the size effect = 0.20 or 20% (minimal size of effect necessary to detect the power 80% and \( \alpha = 0.05 \)). On the basis of these values, we planned to enrol 25 patients per group. We duplicated the size of each group, thus planning to have 50-55 persons per group.

**Randomization.** A randomization list was drawn up by a statistician and forwarded to the Emergency Department. The method for implementing the random allocation was by central telephone. The participants were enrolled by the doctor on call, who was responsible for monitoring the data until 24 h post-burn. Participants were blinded as to group assignment for the duration of the study. The medical personnel who analysed the laboratory data were a blind group.

**Statistical method.** Statistical analysis was performed using SPSS 10.0 for Windows. Mean and standard deviation were used to present continuous data, and the absolute value and percentage were used to present the discrete variables. Baseline measurements of all variables were compared using one-way analysis of variance (ANOVA). Multivariate analysis was conducted with logistic regression (simple and binary) for analysing the causality relationship between variables. Kendall’s correlation coefficient was used to see the relationship between variables. Statistical differences between proportions were compared using the \( \chi^2 \) test. Values of \( p \leq 0.05 \) were considered as showing a statistically significant difference.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LR group 1</th>
<th>LR group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr) ± SD</td>
<td>23.3 ± 24.4</td>
<td>10.7 ± 17.11</td>
</tr>
<tr>
<td>Children</td>
<td>30 (54.5)</td>
<td>45 (82)</td>
</tr>
<tr>
<td>Adults</td>
<td>22 (40)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Elderly</td>
<td>3 (5.5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38 (69)</td>
<td>32 (58)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (31)</td>
<td>23 (42)</td>
</tr>
<tr>
<td>TBSA (percentage)</td>
<td>32 ± 17</td>
<td>22.8 ± 9.2</td>
</tr>
<tr>
<td>Burn cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalding</td>
<td>19 (35)</td>
<td>37 (67)</td>
</tr>
<tr>
<td>Flame burns</td>
<td>29 (53)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Electrical burns</td>
<td>2 (3)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Chemical burns</td>
<td>5 (9)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Burn depth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II degree</td>
<td>31 (57)</td>
<td>41 (74)</td>
</tr>
<tr>
<td>III degree</td>
<td>24 (43)</td>
<td>14 (26)</td>
</tr>
<tr>
<td>Inhalation injury</td>
<td>14 (27)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>11 (20)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Hours after burn ± SD</td>
<td>3.1 ± 2.8</td>
<td>4.4 ± 3.1</td>
</tr>
<tr>
<td>Place of injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>49 (89)</td>
<td>52 (94)</td>
</tr>
<tr>
<td>Work</td>
<td>4 (8)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Environment</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Mean hospitalization stay (days) ± SD</td>
<td>12.3 ± 14.5</td>
<td>13.2 ± 3.0</td>
</tr>
<tr>
<td>Mortality</td>
<td>9 (16)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>SIRS</td>
<td>30 (55)</td>
<td>37 (68)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>25 (45)</td>
<td>18 (32)</td>
</tr>
</tbody>
</table>
Results

During a two-year period, a total of 110 patients were included in the study. Enrolment began in January 2003 and ended in January 2005. The baseline demographic and clinical groups are presented in Table I. Fifty-five patients were analysed in each group. RL group 1 comprised 46 surviving patients and 9 died (mortality, 16%), while in the other RL group 50 patients survived and 5 died (mortality, 9%). Two of the deaths in RL group 1 occurred during the period of resuscitation. Other deaths in both groups were related to septic shock.

Our analysis indicates a statistically significant difference between mortality and burn extent ($p = 0.036$), cause of burn ($p = 0.004$), inhalation injury ($p = 0.027$), and comorbidities ($p = 0.015$). A summary of fluid administered over the first 24 h following injury is shown in Table II.

There was a statistically significant difference between the groups regarding fluid load ($4.23 \pm 1.54$ in group 1 versus $3.33 \pm 1.44$ in group 2) ($p = 0.006$). There was no statistically significant difference between the groups regarding cumulative fluid loads, cumulative urine output, and urine output (ml/kg/h).

Sodium balance is given in Table III. Multiple comparisons were used to analyse sodium intake and excretion in mEq/kg. There was a statistically significant difference between groups 1 and 2 with regard to sodium administered ($18.23 \pm 6.02$ vs $9.85 \pm 2.79$) ($p = 0.000$). There was also a statistically significant difference as regards sodium retention ($17.75 \pm 19.55$ vs $6.52 \pm 2.97$) ($p = 0.000$).

NFA in both groups is shown in Fig. 1. As shown in Table II and Fig. 1, there was a statistically significant difference in NFA between the two groups ($p = 0.001$). Values of 20 ml/kg of NFA were achieved in different times in the two groups. In group 1 this value was achieved in the third hour, while in group 2 it was in the ninth hour of resuscitation. In group 1 the values of NFA at the 24th hour were almost three times as high as in group 2.

With regard to morbidity there was no statistically significant difference between the groups in relation to the clinical situation, SIRS, and sepsis. However, in group 1

![Fig. 1 - Net fluid accumulation in the two groups of patients.](image1)

![Fig. 2 - Different types of net fluid accumulation.](image2)
there were complications in 31 cases (56.4%) compared to 17 cases (30.9%) in group 2. Analysis indicates a statistically significant difference between the amount of fluid given and complications ($p = 0.08$). The majority of the patients (70%) who died, in both groups of patients, presented higher NFA values during resuscitation.

The degree of NFA correlated - with a linear positive relationship - with morbidity (Kendall’s $\tau_{br} = 0.143$, $p = 0.019$) and - with a negative relationship - with mortality (Kendall’s $\tau_{br} = 0.234$, $p = 0.001$).

**Discussion**

Among medical matters, one interesting question is “When has burn shock been successfully overcome?” According to Warden, resuscitation is complete when there is no further accumulation of oedema fluid, which generally occurs between 18 and 30 h post-burn. Resuscitation fluids are utilized until the volume of infused fluid needed to maintain adequate urine volume equals the maintenance fluid volume. The maintenance fluid volume required following burn resuscitation include the patient’s normal maintenance volume and evaporative water loss.

In burn shock, resuscitation is complicated by the obligatory condition of burn oedema, and the voluminous transvascular fluid shifts resulting from a major burn are unique to thermal trauma. It is quite clear that the oedema process is accentuated by the resuscitation fluid. The magnitude of oedema is affected by the amount and type of fluid administered. The National Institute of Health, in the Consensus Summary on fluid resuscitation, recommends that the volume infused should be continually titrated so as to avoid both under- and over-resuscitation.

NFA, defined as cumulative infused fluid volume minus cumulative urine output measured at each interval of resuscitation, helps in achieving the goal of initial burn resuscitation: restoring cardiovascular function and tissue perfusion and avoiding excessive oedema. This suggests that any therapy that can achieve equal or better cardiovascular function with less fluid accumulation would result in a better clinical response to trauma. According to Geir, when NFA reaches 20 ml/kg, that is an indication of the onset of rebound fluid accumulation.

**A brief synopsis of key findings**

Regarding epidemiology, the extent of the patients’ burn ranged from 10 to 60% BSA, with an average of 32 ± 17% in group 1 and 22.8 ± 9.2% in group 2. These data are explained by the fact that most of the cases in group 2 (i.e. 80%) were children aged 0 to 14 years, who required resuscitation even though the burn size was between 10 and 20% BSA, while there were more adults in group 1 with flame burns. If we consider gender, males predominated (60% of the total number in both groups). In group 1 flame burns represented more than half the cases, while in group 2 burns caused by scalds predominated (70% of cases). Regarding burn depth, second-degree burns predominated in both groups, while full-thickness burns in group 1 were twofold compared with group 2. The incidence of inhalation injury and the presence of comorbidities were higher in group 1, with the majority of the burns occurring in a domestic environment.

Regarding fluid load, in group 1 we gave the amounts recommended by the formulas or more. This group included adult cases with flame and inhalation burns that needed more fluid to achieve adequate resuscitation. The reduction of the fluid load in group 2 was, we believe, due to careful monitoring of urine and of clinical signs. The infusion rate was titrated on the urine output rate.

Urine output is an adequate parameter for the evaluation of systemic perfusion, but we think it impossible to expect precise values from it. The average urine output in our study was similar (1.7 ± 0.9) in the two groups. The reason for these values in group 1 was the higher amount of fluid given, while in group 2 it was the result of careful monitoring during resuscitation. We considered this to be positive because very precise values, for individual reasons, can lead to lower values of urine output and to the probability of the presence of oliguria.

NFA is an important parameter for monitoring the fluid balance. As already said, the degree of fluid accumulation correlates with the gravity of the thermal injury and with clinical outcome. Our data support this finding, and patients with a poor prognosis had higher values of NFA. In our groups, net fluid progressively increased in group 1 despite good urine output. In group 2 there were constant values of NFA between 20 and 40 ml/kg. These values testify to the controlled amount of fluid given and to good urine output. Resuscitation is complete when there is no accumulation of oedema fluid (between 18 and 30 h post-burn). We noticed a decrease in the rhythm of the increase in net fluid about 16 h post-burn.

We observed different types of NFA, as follows:

- NFA below 20 ml/kg, testifying to a good clinical situation accompanied by better feeding, because we recorded only fluids given intravenously;
- NFA progressively increasing, as with group 1 patients. In these cases the value of 20 ml/kg was reached early, after 4 or 5 h of resuscitation;
- NFA with a steady increase. In these cases the value of 20 ml/kg was reached after 13 to 16 h of resuscitation and remained for some hours at these values.

**Comparison with relevant findings from other published data**

First we want to compare the results in our two groups of patients with those of our previous studies. The values
ranged from 3.4 ml/kg/% BSA to 4 ml/kg/% BSA and 4.7 ml/kg/% BSA. Warden held that the quantity of crystalloid resuscitation needed was in part dependent on the parameters used to monitor resuscitation. Thus, if higher urine output is considered to indicate adequate perfusion, more fluid will be needed. Generally speaking, the literature supports resuscitation with the smallest volume possible or encourages hyperdynamic resuscitation. Our values for the fluids given in group 2 were 3.3 ml/kg/% BSA, which is consistent with the opinion that permissive hypovolaemia appears to be safe and well tolerated by burn patients. In one study resuscitation was performed with 3.2 ± 0.7 ml/kg/% BSA, while another study recommended higher values than Parkland.

When evaluating the fluid loads needed for burn shock resuscitation, we must take into consideration the presence of full-thickness burns, regardless of weight and burn size. One reason for our being able to reduce fluid loads in group 2 was that only 20% of the burn size was full-thickness, the presence of which increases fluid requirements.

Regarding the resuscitation of children, higher and similar values have been recommended.

In our study, fluid retention was comparable with that reported in some other studies in which the reduction of fluid accumulation was due not to differences in urine output or insensible loss but solely to the difference in retained fluid.

This study was to some degree limited by certain factors. For various reasons, we did not perform any invasive monitoring, which would have helped us during resuscitation of the burn patients. It would also have been better if the sample size had been greater and the laboratory data more expanded, especially in the evaluation of plasma lactate as a significant marker of shock and resuscitation.

We performed a simple randomization of the patients but no precise restricted randomization. In further studies we shall devote greater attention to this aspect and to the analysis of morbidity, mortality, and quality of life in burn patients.

Conclusions

The resuscitation of burn patients is very important and requires the greatest of devotion from the medical staff. The main thing to do is to calculate TBSA precisely and recommend the amount of fluids required for resuscitation. The monitoring of fluid balance creates a positive effect during burn shock resuscitation, avoiding extravasation and oedema. Titrating the fluid rate in relation to clinical signs and urine output should help us create a successful and specific therapy for each burn patient. Observing NFA every hour of therapy keeps us informed of the patient’s clinical situation and, together with other important variables, can help us understand the resuscitation better. As soon as a value of 20 ml/kg is reached, it means that the patient has received fluids at a high rhythm. It is better if this value is reached in the second 8 h of resuscitation. Values of NFA over 20 ml/kg are very important for the subsequent amounts of fluids given. It is better to maintain approximately the same values. Higher NFA values suggest non-suitability of the resuscitation, which includes the possibility of inadequate rehydration. This situation should be taken into account only when we consider its effect on outcome. In the light of this study we support the belief that there is a relationship between NFA and mortality because in both groups most of the cases with a bad prognosis presented higher values of NFA during resuscitation.
me point final primaire était 16% dans le groupe 1 et 9% dans le groupe 2. Donner la quantité de fluides la plus petite possible peut être la manière la plus efficace pour créer une thérapie positive et spécifique pour tous les patients atteints de brûlures. Pour ce qui concerne la morbidité et la mortalité, les facteurs prédictifs, comme aussi la méthode de réanimation, contribuent à maintenir constantes les valeurs de l’accumulation nette des fluides.

BIBLIOGRAPHY


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