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Decreased fluid volume to reduce organ damage: A new approach to burn shock resuscitation? A preliminary study☆

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Summary
Objective: To evaluate the impact of decreased fluid resuscitation on multiple-organ dysfunction after severe burns. This approach was referred to as ''permissive hypovolaemia''.
Methods: Two cohorts of patients with burns >20% BSA without associated injuries and admitted to ICU within 6 h from the thermal injury were compared. Patients were matched for both age and burn severity. The multiple-organ dysfunction score (MODS) by Marshall was calculated for 10 days after ICU admission. Permissive hypovolaemia was administered by a haemodynamic-oriented approach throughout the first 24-h period. Haemodynamic variables, arterial blood lactates and net fluid balance were obtained throughout the first 48 h.
Results: Twenty-four patients were enrolled: twelve of them received the Parkland Formula while twelve were resuscitated according to the permissive hypovolaemic approach. Permissive hypovolaemia allowed for less volume infusion (3.2 ± 0.7 ml/kg/% burn versus 4.6 ± 0.3 ml/kg/% burn; $P < 0.001$), a reduced positive fluid balance ($+7.5 \pm 5.4$ l/day versus $+12 \pm 4.7$ l/day; $P < 0.05$) and significantly lesser MODS Score values ($P = 0.003$) than the Parkland Formula. Both haemodynamic variables and arterial blood lactate levels were comparable between the patient cohorts throughout the resuscitation period.
Conclusions: Permissive hypovolaemia seems safe and well tolerated by burn patients. Moreover, it seems effective in reducing multiple-organ dysfunction as induced by oedema fluid accumulation and inadequate O_2 tissue utilization.

Introduction

Resuscitation from burn shock is a formidable challenge for intensive care specialists. The extensive capillary damage which follows thermal injury

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is responsible for massive plasma extravasation into burned tissues with consequent hypovolaemia and shock.[1–3] Too vigorous resuscitative efforts may lead to severe protein depletion with further oedema accumulation into both burned and unburned tissues. In the past decades several formulae have been developed for optimal fluid resuscitation of burn patients, the most popular being the Parkland Formula.[4] This time-honoured approach allows for sufficient vital organ perfusion, while avoiding excessive oedema formation.

Although adequate resuscitation has long been recognised as the single most important therapeutic intervention of burn critical care, the routine use of invasive haemodynamic monitoring has never been recommended as guide for fluid volume replacement by fear of infections. Nowadays, the adequacy of resuscitative efforts is still assessed by a combination of both traditional and semi-invasive variables, the insertion of a pulmonary artery catheter being restricted to patients with refractory shock or limited cardiopulmonary reserve.[5] In recent years, the introduction of trans-pulmonary indicator dilution technique at the bedside has made the use of invasive haemodynamic monitoring in burned patients easier.[6–8] Its reduced invasiveness as compared with pulmonary artery catheterisation[9] and the possibility of direct cardiac preload estimation[10] also allowed for a haemodynamic-oriented approach to burn shock resuscitation.[6] Since 2000, we routinely use both intrathoracic blood volume (ITBV) and cardiac output measurement as earlier and more sensitive indicators of critical hypovolaemia than vital signs, hourly urine output and central venous pressure. The trans-pulmonary indicator dilution technique enabled us to appreciate that the Parkland Formula did not allow for the early (<24 h) correction of intravascular volume deficit as complete ITBV normalisation could only be achieved after the first 48 h post-burn. Additionally, a condition of fluid unresponsiveness was present throughout the first 12-h period, any increase of the administered fluids only accelerating post-burn oedema accumulation. In a recent study, the rate of intravascular volume replacement was found to be independent from the amount of crystalloid infused as the administration of supranormal volumes failed into the early (24 h) achievement of normal preload and DO_2 values.[8] We therefore speculated that the adoption of a reduced rather than aggressive approach was preferable as the potential existed for decreased oedema formation, provided that resuscitation was not delayed. Since 2004, we therefore reduced the volume given as low as possible by titrating the infusion rate to a minimum ITBV value that allowed for sufficient vital organ perfusion, while at the same time avoiding any resuscitation delay. This approach was referred to as permissive hypovolaemia. We also hypothesised that if the deliberate reduction of resuscitation volume could allow for decreased extravasation of fluids, then less multiple-organ dysfunction might be anticipated as consequence of reduced oedema formation. Therefore, the present study evaluates the effectiveness of permissive hypovolaemia in reducing multiple-organ dysfunction as compared with the Parkland Formula.

Methods

The study was performed in accordance with guidelines laid down by the hospital ethics committee

Two cohorts of patients were compared. Twelve patients resuscitated with permissive hypovolaemia and admitted to our eight general ICU beds from January 2004 to December 2005 were matched with 12 patients receiving the Parkland Formula in the two preceding years. Patients were enrolled only if they were equipped with the PiCCO© system (Pulsion Medical System, Munich, Germany) thus allowing for both ITBV and cardiac output measurements. Other admission criteria were age >14 years, burn size $\geq$20% BSA, absence of concomitant injuries and ICU admission within 6 h of the thermal insult. Exclusion criteria were inhalation injury as confirmed by bronchoscopy, pre-existing medical illnesses compromising the cardiopulmonary reserve and need for compassionate care only. As cardiovascular reserve and trauma severity are important determinants of multiple-organ dysfunction, the makeup of both cohorts was matched for age, total burns size and depth thus providing an accurate comparison of the two infusion regimens that was not affected by these factors. Additionally, patients receiving the Parkland Formula were included only if their actual resuscitation volume was lesser than 5 ml/kg/% burn. The different impact of permissive hypovolemia and the Parkland Formula on multiple-organ dysfunction was our primary study end-point. The multiple-organ dysfunction score (MODS) by Marshall et al. was used to assess the severity of organ function impairment.[11] The score was calculated on a daily base for 10 consecutive days. Cardiac preload as assessed by thermo-dilution derived ITBV measurement and continuous cardiac output monitoring by femoral arterial thermo-dilution calibrated pulse contour analysis[12] were obtained

throughout the first 48 h period. The severity of tissue hypoperfusion was assessed by arterial blood lactate measurements. Systemic vascular resistance (SVR), ventricular stroke volume (SV) and global oxygen delivery (DO_2) were calculated using standard formulae and indexed to body surface area, thus allowing for inter-individual comparison. Daily urine output was recorded and expressed as ml/kg/day. Daily evaporative losses were estimated according to the formula: [3750 ml × BSA (m^2) × (% burn/100)]: thus an adult of 2 m^2 with a 20% burn extension had a calculated water loss of 3750 ml × 2 × 0.20 = 1500 ml/day. Net fluid balance was calculated as the algebraic sum of the total volume given minus the daily urine output and evaporative water losses. The fluids administered before ICU admission were included into the calculations of the total resuscitation volume.

Resuscitation protocol

Patients resuscitated according to the Parkland Formula received 4 ml/kg/% burn of Ringer's lactate solution as the first instalment of their anticipated volume requirements. The infusion rate was adjusted to achieve an hourly urine output between 0.5 and 1 ml/kg/h and mean arterial pressure values greater than 70 mmHg. Continuous cardiac output monitoring allowed for the early detection of critical hypovolaemia as diagnosed by a reduction of cardiac index below 2.0 l/min/m^2 provided that CVP value was less than 4 mmHg. In patients receiving permissive hypovolaemia the first half of the resuscitation period was addressed to achieve the best compromise between minimum fluid extravasation and sufficient vital organ perfusion. Thereafter, resuscitative efforts were directed to achieve the progressive correction of intravascular volume deficit. Therefore, the first 12-h volume was reduced as low as possible by titrating the infusion rate to the minimum ITBV value that allowed for at least 2.2 ± 0.2 l/min/m^2 of cardiac index, as this was the threshold value that ensured no less than 0.5 ml/kg of hourly urine output. Thereafter, a constant volume of infusion was administered throughout the second 12 h period by calculating a steady value of hourly infusion rate as the average amount of hourly volume requirements over the last 3-h period. A pulse-dose of 250 ml hydroxyethylstarch solution was added to both infusion regimens whenever critical hypovolaemia developed. The dose was eventually repeated until the cardiac index rose above 2.0 l/min/m^2 provided that CVP value was lesser than 10 mmHg. After the first 24-h period each patient received a maintenance fluid volume calculated as follows: [1500 ml × BSA (m^2)] + [3750 ml × BSA (m^2) × (%burn/100)]. The maintenance fluid volume was given as 50% normal saline in 5% dextrose solution. According to the practice guidelines for burn care,[13] successful resuscitation was achieved when no further oedema fluid accumulation occurred, this in practice meaning that a neutral balance was achieved between actual and maintenance fluid volume. Patients with severe plasma protein depletion (<3.5 g/dl) received 20% albumin in saline solution after the first 24 h post-burn. Fresh frozen plasma and packed red cells were utilized as appropriate.

Data analysis

The area under curve (AUC) of the daily MODS score was calculated throughout the first 10 days after ICU admission and also used for analysis.[14] Data were expressed as means ± S.D. or number and proportions. Skewed data were summarised as medians and inter-quartile range (IQR). Continuous values were compared using Student's *t*-test or the Mann—Whitney test, depending on their distributional properties. Difference in proportions was compared with use of the Fisher's exact test. Covariance analysis was used to adjust for the effect of confounding variables on the outcome measure. The relationship between oedema fluid accumulation and severity of multiple-organ dysfunction was analyzed by linear regression analysis. ANOVA for repeated measurements was used to investigate the time profile and time by group interactions of independent variables. Post hoc analysis was performed by the Tukey's test. $P < 0.05$ was considered significant.

Results

Table 1 lists both demographics and main burn characteristics for the patient cohorts. By design, mean age ($P = 0.31$), total burn surface area ($P = 0.90$) and full-thickness burn depth ($P = 0.78$) were similar between groups.

Type and amount of administered fluids

Both the amount and type of administered fluids are detailed in Table 2. The actual resuscitation volume given using the Parkland Formula averaged 4.67 ± 0.31 ml/kg/% burn (range 4.1—4.9 ml/kg/% burn), with half of that amount being given during the first 8 h (Figure 1). Conversely, permissive hypovolaemia made allowance for only

Table 1 Main patients' characteristics on admission

	Permissive hypovolaemia	Parkland Formula
Age (years)	40 ± 14	47 ± 17
Total burn extension (% body surface area)	48 ± 22	49 ± 22
Full thickness burn wound depth (% body surface area)	27 ± 28	23 ± 27
Burn source		
Flame	10	10
Explosion	1	2
Others	1	–
Weight (kg)	76 ± 16	72 ± 18
Sex (M/F ratio)	10/2	11/1
Time delay before ICU admission (min)	66 ± 29	63 ± 25
Pre-hospital fluid Volume (ml)	1000 ± 900	800 ± 990
Mechanical ventilation (patients)	12/12	10/12
Near-circumferential burns (patients)	7	6
Escharotomy/fasciotomy (patients)	2	4

Results are expressed as numbers or mean ± S.D.

3.2 ± 0.75 ml/kg/% burn to be given ($P < 0.0001$). The pattern of fluid administration also differed between groups as permissive hypovolaemia allowed for about 50% reduction of the first 12-h volume with respect to the Parkland Formula (Figure 1). Thereafter, no further volume reduction was performed throughout the second 12-h period, so that the amount of administered fluids was similar between groups. As expected, the reduced volume of crystalloids did not affect urine production as an hourly urine output between 0.5 and 1.0 ml/kg/h was obtained during the infusion of both resuscitative regimens (Figure 2). Nevertheless, permissive hypovolaemia produced a smaller positive fluid balance ($P < 0.05$), this in turn leading to less oedema fluid accumulation than the

Table 2 Type and amount of fluids volume replacement, hourly urine output and net fluid balance throughout the first 48-h period

	Permissive hypovolaemia	Parkland Formula	*P* value
Resuscitation volume (0–24 h) (Ringer's lactate solution) (ml/kg/% burn)	3.2 ± 0.75	4.67 ± 0.31	<0.0001
Maintenance fluid volume (24–48 h) (50% normal saline in 5% dextrose) (ml/kg/%burn)	2.28 ± 1.08	2.17 ± 0.69	NS
Hourly urine output (0–24 h) (ml/kg/h)	1.0 ± 0.4	1.3 ± 0.6	NS
Net fluid balance			
0–24 h	+7.5 ± 5.4	+12.0 ± 4.7	<0.05
24–48 h (l/day)	−0.4 ± 2.6	0.6 ± 2.9	NS
Critical hypovolaemia (250 ml hydroxyethylstarch)			
• Patients (number)	3	3	NS
• Episodes (number)	6	5	–
• Doses (number)	11	13	–
• Timing:			
(0–8 h)	8	2	0.01
(8–16 h)	3	2	
(16–24 h)	0	9	
20% Albumin in saline solution			
• Patients (number)	4	7	NS
• Volume* (ml)	200 (175–250)	150 (100–300)	NS

Results are expressed as mean ± S.D. or median and IQR (*) as indicated.

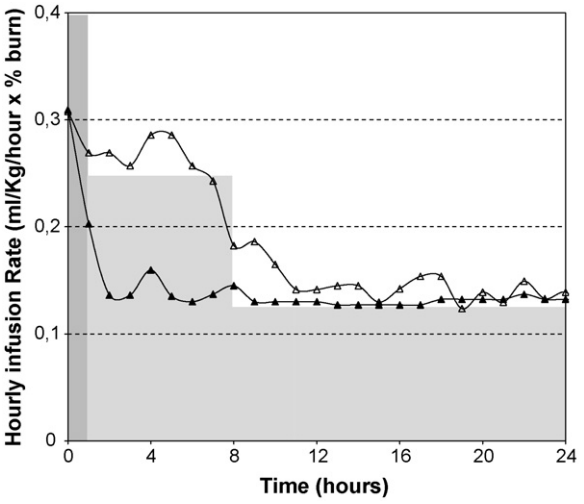

Figure 1 Time profile of fluid administration (ml/kg/h % burn) in patients receiving Parkland's Formula (open triangles) and permissive hypovolaemia (closed triangles). Data are median values. Light area represents the recommended pattern of hourly infusion rate as anticipated by Parkland Formula. The median time before ICU admission is shown as dark area.

Parkland Formula. No resuscitation delay occurred by permissive hypovolaemia as the net fluid balance between the actual and the maintenance fluid volumes averaged null values in both patient cohorts. The rate of early (<24 h) complications was similar between groups. Neither serum creatinine nor intra-abdominal pressure increased throughout the resuscitation period. Escharotomy incisions were needed in six patients only after a median time of 18 h (IQR 13.7—24 h). Critical hypovolaemia developed in six patients (three from each group) although it occurred earlier ($P < 0.01$) during permissive hypovolaemia than the Parkland Formula (Table 2). The excessive reduction of resuscitation volume during the early (<8 h) post-burn period was responsible for critical hypovolaemia in patients receiving the permissive hypovolaemic approach, while serious plasma losses through the escharotomy incisions caused it later (>16 h) during the Parkland Formula.

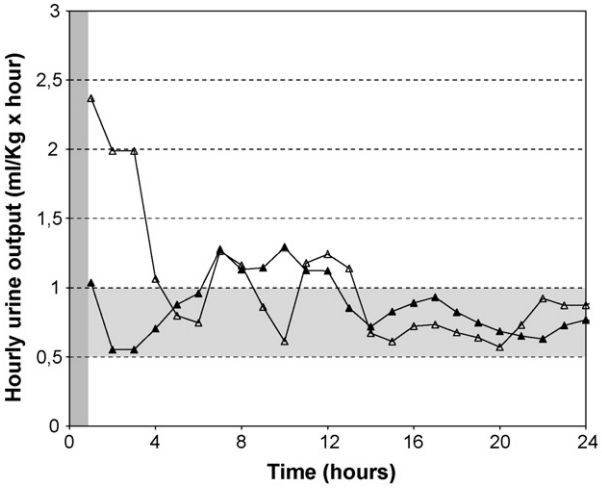

Figure 2 Time profile of hourly urine output (ml/kg/h) during administration of Parkland Formula (open triangles) and permissive hypovolaemia (closed triangles). Data are median values. Light area represents the desired range of hourly urine output during the resuscitation period. The median time before ICU admission is shown as dark area.

Haemodynamic profile

Table 3 shows the time profile of haemodynamic variables throughout the first 48 h. On average both patient cohorts showed lower than normal ITBV values, decreased cardiac output measurements and elevated systemic vascular resistances on admission. As expected, the haemodynamic pattern did not change with either resuscitative regimen during the first 12-h. Thereafter, all haemodynamic variables increased towards normal values with a significant time effect for both cardiac output and its related variables. No inter-group differences were observed for any of haemodynamic varaibles at the indexed times (Table 3).

Biochemical variables

On average, the biochemical impact of the two resuscitative regimes was similar as comparable serum sodium, plasma protein, arterial blood lactate and haematocrit profiles were obtained throughout the first 48-h period.

Multiple-organ dysfunction

The median profile of MODS Score results is shown in Figure 3. On admission, both groups showed similar values, but thereafter a steeper increase of MODS Score was observed in patients receiving the Parkland Formula. As result, the area under curve measurement significantly differed between groups ($P = 0.003$) with higher values being found in the Parkland Formula (29.5 ± 7.5 points) than permissive hypovolaemia group (10.7 ± 7.8 points). The respiratory component of the score was mainly responsible for this difference (9.6 ± 4.7 points versus 2.8 ± 3.9 points; $P = 0.026$). The severity of multiple-organ dysfunction correlated with the amount of fluids given (Figure 4), as the larger was the infused volume, the higher was severity of organ function impairment ($R^2 = 0.45$; $P < 0.005$).

Table 3 Time profile of semi-invasive and invasive haemodynamic variables during the first 48 h post-burns

Parameters	Group	0—4 h	4—8 h	8—16 h	16—24 h	24—48 h
Core temperature (°C)	PH	35.3 ± 1.3	36.0 ± 1.3	37.4 ± 0.9	37.3 ± 0.9	37.1 ± 1.4
	PF	35.1 ± 1.8	36.0 ± 1.5	37.3 ± 1.0	37.2 ± 0.8	37.1 ± 0.8
MAP (mmHg)	PH	80 ± 12	83 ± 18	91 ± 15	88 ± 11	91 ± 12
	PF	92 ± 12	90 ± 13	93 ± 11	89 ± 10	92 ± 10
CVP (mmHg)	PH	3.3 ± 2.8	3.0 ± 1.9	3.2 ± 3.2	3.0 ± 2.5	2.8 ± 2.4
	PF	2.3 ± 3.4	3.9 ± 2.8	2.7 ± 3.2	2.9 ± 2.4	3.1 ± 2.9
HR (bmp)	PH	91 ± 22	99 ± 19	101 ± 20	103 ± 19	104 ± 17
	PF	98 ± 22	102 ± 26	107 ± 25	108 ± 18	107 ± 16
CI (l/min/m^2)	PH	2.6 ± 0.7 (*)	2.6 ± 0.5 (#)	3.2 ± 0.8 (§)	3.4 ± 0.7	4.3 ± 1.0
	PF	2.1 ± 0.6 (*)	2.4 ± 0.3 (#)	3.1 ± 0.5	3.1 ± 0.7	3.4 ± 0.9
SVI (ml/m^2)	PH	29 ± 10 (*)	26 ± 9	31 ± 7	30 ± 10	42 ± 13
	PF	32 ± 12 (*)	31 ± 10 (#)	31 ± 6	35 ± 12	35 ± 12
DO_2I (ml/min/m^2)	PH	574 ± 172 (*)	562 ± 85 (#)	685 ± 161	645 ± 104	752 ± 135
	PF	584 ± 38 (*)	546 ± 93 (#)	640 ± 117	645 ± 202	722 ± 186
SVRI (dyne/s/cm^5)	PH	3137 ± 1093 (*)	2794 ± 789	2436 ± 627	2383 ± 981	1885 ± 609
	PF	3176 ± 423 (*)	3094 ± 516(#)	2121 ± 462	2644 ± 695	2148 ± 600
ITBVI (ml/m^2)	PH	654 ± 174	691 ± 157	678 ± 319	704 ± 103	755 ± 132
	PF	685 ± 213	763 ± 212	704 ± 164	765 ± 153	793 ± 112
EVLWI (ml/kg)	PH	7.6 ± 3.8	6.4 ± 1.5	6.3 ± 1.3	5.6 ± 2.7	5.8 ± 2.5
	PF	6.8 ± 2.0	5.8 ± 1.9	6.5 ± 1.7	6.7 ± 1.9	7.2 ± 3.1
Arterial blood lactate (mmol/l)	PH	1.80 ± 0.89	2.54 ± 1.15	1.98 ± 1.49	1.97 ± 1.24	1.93 ± 0.63
	PF	3.62 ± 2.03	3.93 ± 1.97	2.42 ± 0.96	3.23 ± 2.25	2.45 ± 1.45

PH: permissive hypovolaemia, PF: Parkland Formula, MAP: mean arterial pressure, CVP: central venous pressure, HR: heart rate, CI: cardiac index, SVI: indexed stroke volume, SVRI: indexed systemic vascular resistance, ITBVI: indexed intra-thoracic blood volume, EVLWI: indexed extra-vascular lung water volume. Results are expressed as means ± S.D. ANOVA results: $P < 0.05$; comparison of last vs. first (*), second (#) and third (§) column.

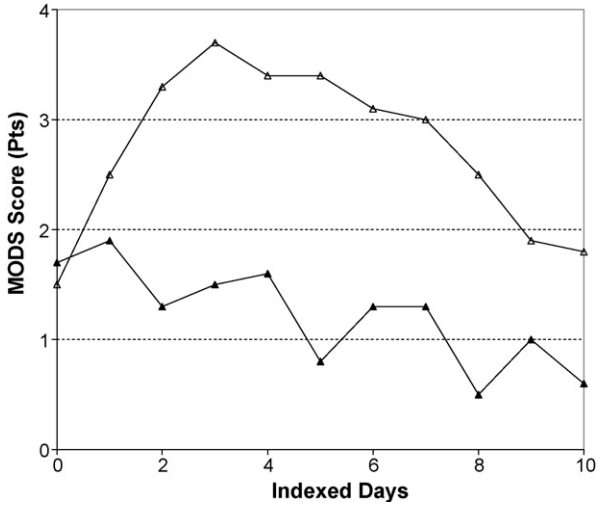

Figure 3 Median results of MODS Score throughout the first 10 days post-burn in patients resuscitated according with Parkland Formula (open triangles) and permissive hypovolaemia (closed triangles).

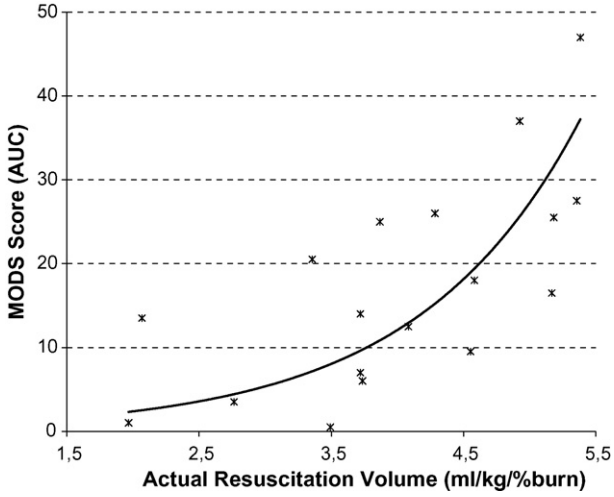

Figure 4 Relationship between the total amounts of administered fluid volume expressed as ml/Kg/% burn and area under curve (AUC) measurement of MODS Score. According with the curvilinear relationship the larger was the amount of administered fluids the more severe was the resulting multiple-organ dysfunction ($R^2 = 0.45$; $P < 0.05$).

Discussion

The main study result is that resuscitation volume can be safely reduced below the Parkland estimate, provided that reduction of administered fluids is guided by close haemodynamic monitoring. Additionally, we provide the first objective evidence that post-burn oedema is detrimental to organ function and that such a deleterious effect is proportional to the amount of extravasated fluids. Permissive hypovolaemia allowed for 3.2 ± 0.75 ml/kg/% burn of total resuscitation volume against an anticipated requirement of 4.0 ± 0.3 ml/kg/% burn.[15] However, the reduction of fluids given did not cause any resuscitation delay as the haemodynamic pattern of both patient cohorts normalised within the same time interval (Table 3). In addition, the haemodynamic profile was not at variance throughout the resuscitation period despite the large difference in fluids given. This was not unexpected, as the increase of capillary permeability during the early post-burn period may overcome even the most aggressive infusion regimen. A resuscitation volume of 8 ml/kg/% burn has recently been reported to fail in the early (24 h) achievement of normal preload values.[8] It has been speculated that the insensitivity of cardiac preload to increase by even the most aggressive regimens might derive from the combination of both increased capillary permeability and higher hydrostatic pressure than most forms of hypovolaemic shock.[16] Therefore, a supra-normal resuscitation volume might exacerbate post-burn oedema accumulation by unnecessarily increasing both the amount and length of fluid extravasation. In this sense permissive hypovolaemia is innovative as it aims at post-burn oedema reduction by decreased resuscitation volume rather than earliest correction of intravascular volume deficit by supra-normal fluid administration.[6–8,17–19] According to our hypothesis, the reduction of volume given was obtained throughout the period of maximum capillary damage (Figure 1). However, this would be impossible without the use of invasive haemodynamic monitoring as both ITBV and cardiac output measurements generated important physiologic information which could not be otherwise calculated or inferred by traditional monitoring variables.[20] The MODS Score by Marshall et al.[11] was used to verify the hypothesis that fluid volume reduction lead to decreased oedema formation and hence less organ dysfunction. As expected, lower MODS Score values were obtained by permissive hypovolaemia as compared with the Parkland Formula ($P < 0.003$). Notably, a quantitative relationship existed between the infused volume and severity of organ function impairment (Figure 4). Several findings suggest a causative role for post-burn oedema in the early development of multiple-organ dysfunction. Firstly, the mild and transitory elevation of MODS Score in the early post-burn period could hardly be attributed to severe sepsis or septic shock as these are usually later complications with severe and persistent organ damage. Furthermore, the mild respiratory dysfunction we observed in our patients probably results from decreased chest-wall compliance from inelastic burn tissue and soft tissue oedema as reflected by repeatedly normal EVLW measurements. This is in agreement with the normally reported function of the pulmonary capillary membrane during the immediate post-burn period.[21] In the present study, a selective use of colloid-containing solution was performed. Therefore, synthetic colloids were used throughout the resuscitation period in order to correct plasma volume deficit, while 20% albumin was given after crystalloid resuscitation in an attempt to attenuate the loss of oncotic power with the least amount of volume fluids. A plasma protein level of 3.5 gr/dl, that is an albumin level of about 2.0 gr/dl, was chosen as the threshold value for plasma protein replacement in our patients. Although lower cut-off values are usually adopted in critically ill patients with no thermal injuries, this conservative approach was chosen as we feared the excessive reduction of plasma protein levels throughout the post-resuscitation period. As abnormal capillary permeability does not cease abruptly but it attenuates after the first 24-h period, we reasoned that further protein depletion might result into dangerous reduction of plasma oncotic power with increased risk for loss of arterial pressure control[22] and compartment syndrome development.[23] We are aware of our study limitations due to its lack of prospective design. In fact, neither were patients prospectively assigned to receive a randomised resuscitative regimen nor was the Parkland Formula guided by predetermined haemodynamic end-points as occurred with permissive hypovolaemia. Therefore, although biologically plausible, we can only argue about the causal relationship between reduced post-burn oedema and decreased severity of organ function impairment. In other words, we cannot exclude that patients requiring more fluids did so because of more severe organ derangement. Despite these limitations, we believe our results are important as, if confirmed by properly planned studies, permissive hypovolaemia might be the most suitable approach for clinical conditions where increased permeability with or without elevated filtration pressure

coexist. The small number of patients studied is another limitation of the present study as its statistical power may be decreased. However, we believe that the detailed description we offered of both the physiological and time-dependent aspects of fluid volume reduction largely compensate for the smallness of sample size.

Conclusions

Permissive hypovolaemia seems to be effective in reducing both organ and system dysfunction as induced by oedema accumulation. This haemodynamic-oriented resuscitative approach allows for a better refinement of fluids volume administration during the very early post-burn period thus minimising unnecessary fluids overload.

Conflict of interest statement

The authors state that no financial or personal conflict of interest exists with regard to the present study.

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