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Hydroxyethylstarch supplementation in burn resuscitation—A prospective randomised controlled trial

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ABSTRACT

Introduction: Hydroxyethylstarches (HES) are thought to be beneficial in trauma and major surgery management, due to their volume expansion and anti-inflammatory properties. This study examined the use of 6% (HES) in burn resuscitation.
Methods: 26 adult patients with burns exceeding 15% total body surface area (TBSA) were randomised to either crystalloid (Hartmann's solution) or a colloid-supplemented resuscitation regime, where 1/3 of the crystalloid-predicted requirement was replaced by 6% HES.
Results: There was no difference in age, gender or TBSA between the two groups. The median (95% CI) fluid volume/%TBSA received in the first 24 h was 307 ml and 263 ml for the crystalloid only and HES-supplemented group respectively ($p = 0.0234$, Mann–Whitney). Body weight gain within the first 24 h after injury was significantly lower in the HES-supplemented group 2.5 kg versus 1.4 kg respectively ($p = 0.0039$). The median (95% CI) serum C-reactive protein at 48 h after injury was 210(167–257) and 128(74–145) mg/L for the crystalloid only and HES-supplemented group respectively ($p = 0.0001$). Albumin–creatinine ratio per % burn (ACR, a marker of capillary leak) was lower in the HES-supplemented group at 12 h after burn ($p = 0.0310$).
Conclusions: Patients treated with HES-supplemented resuscitation required less fluid, showed less interstitial oedema and a dampened inflammatory response compared to patients receiving isotonic crystalloid alone.

1. Introduction

In the 40 years since Baxter's animal experiments for the development of the Parkland formula, research has been devoted to its refinement as well as the advent of other resuscitation formulae, with relatively less interest into what constitutes the most effective choice of fluid. A survey of 140 US burns centres showed that 78% used Ringer's lactate during the first 24 h according to the Parkland formula [1]. Boldt and Papsdorf more recently carried out a survey of current trends in burns resuscitation across Europe. Of the 120 burns units surveyed, 58% use crystalloid with only 12% adhering strictly to the Parkland formula. Albumin is the preferred fluid choice in 17% of units and a mere 4% include hydroxyethylstarch in their resuscitation regime. When it comes to rescuing situations of hypovolaemia during burn resuscitation, 64% of European units resort to human albumin solution, 53% to hydroxyethylstarch and 45% persevere with crystalloid [2].

Following the 1998 Cochrane Review meta-analysis practice is slowly changing as confidence in albumin has

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decreased. Protein solutions in the early shock phase period were deemed to be as effective as crystalloid and may have even been responsible for a detrimental accumulation of lung water [3]. One of the criticisms of the reviews, however, was that all the colloids were grouped under the same umbrella [4]. Cochran et al. in a case–control study of 101 burns-resuscitated patients, actually showed albumin to be protective in a multivariate model of mortality. Part of the reason why albumin-treated patients may have displayed worse prognosis in retrospective trials, is that they tend to have suffered more severe injuries and are as a result, more systemically unwell [5]. Is it time to re-consider certain colloids? Goodwin et al. recommend the delay of protein solutions beyond the first 24 h after burn, whereas others administer colloids from the beginning along with crystalloid.

The most widely accepted burn fluid resuscitation regime in use today is undoubtedly the Parkland formula, but a number of recent studies have shown that the formula underestimates fluid requirement in approximately 50% of cases [6–8]. Augmentation of crystalloid intake has led to the phenomenon of ''fluid creep'', initially described by Pruitt, with associated morbidity. An excellent review of the phenomenon by Saffle has highlighted the fact that the original Parkland formula relied on colloid boluses after 24 h [9]. This raises the question; why not formally include colloids in our current resuscitation regimes or for ''rescue'' resuscitation? ''Permissive hypovolaemia'' is another new concept, an attempt to counterbalance the ''fluid creep'' and minimise the formation of excessive oedema. This has only been possible with meticulous haemodynamic monitoring and the early addition of new generation colloids like hydroxyethylstarch [10].

Hydroxyethylstarches have been recognised as effective plasma expanders in acute burn resuscitation since 1989, with haemodynamic and oxygen transport effects equal or superior to those of 5% albumin [11]. Hydroxyethylstarches, however, have more to offer than their volume-expanding properties, they are known to modulate the inflammatory response through interference with cytokine release and interaction of leukocytes with the vascular endothelium [12–14]. These are arguments for the introduction of hydroxyethylstarch as a supplementation strategy, early on in the resuscitation phase, in an attempt to tame the inflammatory response and prevent hypoperfusion. This represents a change from their current role, which is to rescue situations of hypovolaemia refractory to increasing the crystalloid infusion rate. There is increasing evidence that maximising the rate of fluid infusion in the immediate phase after burn may be beneficial to the overall outcome [15].

The aim of the study was to determine the effect of hydroxyethylstarch supplementation on total volume of fluid resuscitation, weight gain, renal function and inflammatory response or vascular endothelial permeability following major thermal injury.

2. Methods

All adult acute burns admissions to the University Hospital Birmingham Burns Centre between May 2004 and May 2006, with injury exceeding 15% total body surface area (TBSA) were considered for inclusion into the study. The exclusion criteria were patient age below 16 or above 80, burn greater than 80% TBSA, pregnancy, transfer delay of more than 6 h from the time of injury, history or biochemical evidence of renal impairment on admission (serum creatinine >130 μmol/L), history or haematological evidence of a bleeding diathesis and failure to obtain consent or assent.

Ethical approval for the prospective randomised control Fluid Resuscitation trial was granted by the Local Research and Ethics Committee.

2.1. *Patient assessment*

The patients were assessed in the Accident and Emergency Department within 15 min of arriving to the UHB Burns Centre. After establishment of airway patency, breathing and circulation, Hartmann's infusion was started, unless already done by the referring hospital or paramedics. The airway was assessed by a senior anaesthetist regarding the need for intubation and ventilation.

Total body surface area (TBSA) burn was estimated with a Lund & Browder chart and confirmed by two members of staff for the immediate adjustment of intravenous fluid resuscitation requirement. The proportion of full thickness burn (FTB) involvement was also calculated. The patients were subsequently catheterised for detailed monitoring of urine output. It was therefore possible to collect hourly urine samples for analysis that detects microalbuminuria (traces of albumin).

2.2. *Patient randomisation*

Adult patients with thermal injury exceeding 15% total body surface area (TBSA), admitted to the UHB Burns Centre over a period of 2 years were included in the study and considered for randomisation into the trial. The randomisation was carried out by means of a sealed envelope system. In view of the trial's small size, block randomisation was chosen to ensure that allocation to each group was evenly balanced at the end of each block of 10 patients. Patients were randomised to one of two arms; crystalloid only or HES-supplemented fluid resuscitation according to the trial protocol. Informed consent or assent by the next of kin for participation in the trial was obtained prior to recruitment and randomisation.

2.3. *Fluid resuscitation regime protocol*

Patients randomised to the ''crystalloid only'' resuscitation arm received Hartmann's solution according to the Parkland formula, which is local practice. For the ''HES-supplemented'' fluid resuscitation arm, one-third of the crystalloid-predicted requirement was replaced by 6% hydroxyethylstarch (Elo-Haes® 200/0.6, Fresenius-Kabi, Bad Homburg, Germany). As the manufacturer recommends a limit of 33 ml/kg/24 h it was not possible for the whole resuscitation volume to be given as 6% HES. The maximum allowed volume was infused in the colloid-supplemented arm patients at a regular rate, halving it at 8 h post-injury when the crystalloid rate was also halved, patient's condition permitting. Elo-Haes was, however, not allowed to exceed one-third of the total resuscitation fluid

volume infused, based on previous colloid-containing fluid regimes (Brooke) and evidence from studies showing the benefit of HES over other colloids. In order to avoid fluid overload (by substituting the volumes like for like) all the published evidence of plasma volume expansion with 6% HES was taken into account. The expansive value of 6% HES is in the region of 1:1.5, in other words the blood volume expansion achieved is 1.5 times the volume of HES infused. The total 6% HES hourly volume allowance was translated into its crystalloid equivalent, by multiplying it by 1.5. The resulting volume was subtracted from the predicted crystalloid requirement for the hour which provided the hourly Hartmann's volume to be infused. This was considered to be safe as it was possible to subsequently increase the infusion volume, if that proved to be inadequate.

The parameters against which the fluid resuscitation was titrated were:

- Urine output: 0.5–1 ml/kg/h in uncomplicated burn injury and 1–2 ml/kg/h in the presence of inhalation injury;
- Mean arterial pressure (MAP) >70 mm Hg; and
- Heart rate (HR) <120 bpm.

The rate of the crystalloid infusion was increased by 10% following inadequate urinary output for more than 2 consecutive hours, after a 200 ml bolus of crystalloid. This adjustment was repeated as required to obtain the desired urine output. When urine output exceeded 2 ml/kg/h the infusion rate was decreased by 10% aliquots accordingly. Oliguria refractory to crystalloid boluses and infusion rate increase was only corrected by colloid when associated with hypotension (MAP <70 mm Hg) and/or tachycardia above 120 bpm. Hydroxyethylstarch boluses for critical hypovolaemia were not withheld from patients in the ''crystalloid only'' arm of the trial. These, however, qualified as study protocol violations and led to the withdrawal of patients from the crystalloid arm of the trial. Escalation to addition of inotropes was also used in cases of hypoperfusion refractory to fluid challenges or infusion rate increase. The preferred first line agent in our institution is noradrenaline. No blood or blood products were used during the 24-h study period.

2.4. Outcome measures

Fluid intake and balance were measured at 24 h after injury along with serum creatinine, albumin, C-reactive protein and base excess on admission and at 12, 24 and 48 h post-injury. Respiratory function was measured during the first 48 h using hourly ventilation/perfusion ratio (PO_2/FiO_2) for ventilated patients and % oxygen saturation from pulse oximetry ($SatO_2$) corrected for inspired oxygen % (FiO_2) in the non-ventilated patients.

2.5. Weight estimation at 24 h post-injury

Weight gain was considered to be an appropriate reflection of the degree of interstitial tissue oedema in patients. Standardisation of patient weighing was ensured through use of a single device, the Eleganza ITU Weighing System (Pegasus LTD., Waterlooville, Hants, UK). The weighing bed frame monitors weight changes with an accuracy of ±50 g. All patients were weighed on admission and again at 24(±4) h post-injury. This took place during the first dressing-change, when all the dressings were removed and the wounds covered with cling-film. In addition there was a single sheet and pillow with pillow-case weighing a total of 1.2 kg. Suspension of the urinary catheter bag from the bed frame excluded its weight from the total patient weight estimation.

2.6. Measurement of urinary albumin

Microalbuminuria was used as an indicator of endothelial dysfunction or capillary leak as previously explained [16]. Serial urine specimens were collected from the urethral catheter. All patients had urinary catheters in situ as part of their routine management. Urine albumin was measured by automated polyethylene glycol-enhanced immuno-turbidimetry using reagents from Roche Diagnostics on a Roche Modular™ automatic analyser (Roche Diagnostics LTD, Lewes, UK). Urine creatinine was measured by O'Leary modification of the Jaffe reaction using alkaline picrate, using the above reagents and analyser. Results were expressed as the albumin/creatinine ratio (ACR) to correct for variations in urine flow rate. Normal values in ambulatory adults are <2.3 mg/mmol.

Hourly urine specimens were collected from each patient, from as early as 2 h after burn, for the first 12 h after injury. The rate of specimen collection was changed to 4-h thereafter until 36 h post-injury. Specimens were stored at 4 °C for analysis by the local biochemistry department.

2.7. Statistical analysis

2.7.1. Power of study calculation

There are no studies to provide a direct comparison between a crystalloid and starch group in burns resuscitation. Previous work has been carried out in the same institution in major trauma and elective abdominal aortic aneurysm surgery. Twenty patients in each treatment group were enough to show a statistical difference at the 95% level with a power of 80% between two types of fluid resuscitation (Gelofusine 4% vs. 6% hydroxyethylstarch) in terms of fluid volume requirement, ACR (capillary leak), serum C-reactive protein, respiratory and renal function [17,18]. This was an extension of previous power calculations, based on the assumption that if a difference was demonstrated between two types of colloid (albeit in a different injury models) a difference between a crystalloid and a colloid regime was likely to be more marked. Predicting the number of patients required to show a difference in weight gain between the two groups was not possible since no previous work had been carried out in this field at the time, this was exploratory in nature.

The ''Analyse it'' statistical package created by Leeds University was used for the statistical analyses of this study. Categorical data was compared using the chi-square test. Normally distributed data was presented as mean and standard deviation or standard error of the mean. For data showing a skewed distribution, medians and inter-quartile ranges were used with the Mann–Whitney *U* test for non-parametric analysis. In order to identify exact time points of

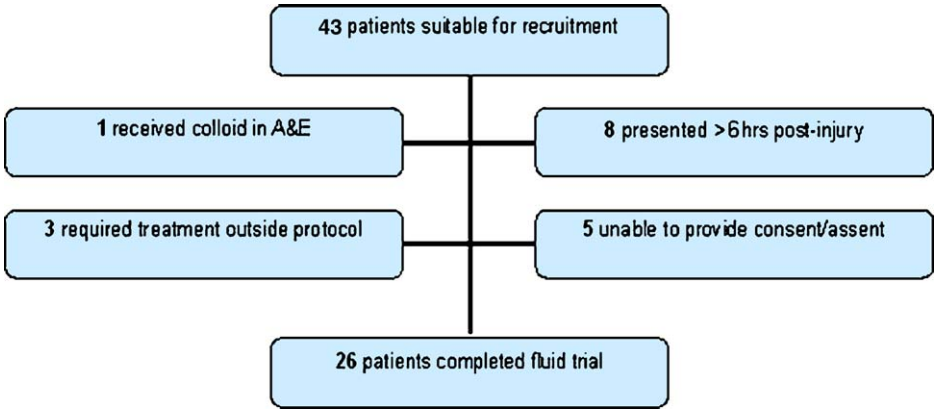

Fig. 1 – Patient recruitment for burns fluid resuscitation randomised control trial.

any difference between the two groups in terms of a potential anti-inflammatory mechanism, values at each time point were compared using the Kruskal–Wallis ANOVA test with Bonferroni correction. A p value of less than 0.05 was indicative of statistical significance for 95% confidence.

3. Results

Of the 43 eligible patients 26 were successfully included in the trial. There was a delay in reaching the burns unit of more than 6 h post-injury in 8 patients. It was not possible to obtain informed consent for participation in a further 5 cases due to intubation prior to transfer (3 patients), intoxication (1 patient) and learning difficulties (1 patient), with no next of kin present to consider or provide assent. One patient had received colloid at the referring hospital and was therefore withdrawn from the trial. A further 3 patients required hydroxyethylstarch boluses for critical hypovolaemia, despite having been randomly assigned to the crystalloid arm. They were therefore withdrawn from the trial, as protocol violations (Fig. 1).

The mean TBSA involvement for the 26 patients was 27% (range 15–62%) with a mean full thickness burn (FTB) involvement of 11.5% (range 0–55%).

The ''crystalloid only'' group consisted of 14 patients that only received Hartmann's for their fluid resuscitation. The ''HES-supplemented'' group of 12 patients received 6% HES in addition to the crystalloid as part of their fluid resuscitation. Hartmann's fluid infusions started upon patient presentation to the accident and emergency department (at a median time of 1.5 h post-injury) whereas 6% HES infusions were only commenced after patient informed consent was obtained. This took place at a median (range) of 4(3–5) h post-injury. HES represented one-third of the total volume requirement in the first 24 h and was administered at a steady rate (not as boluses), the rate was halved after 8 h post-injury.

There was no difference between the two groups in terms of age or sex. The mean age was 42.4 for the ''crystalloid only'' and 40.8 for the ''HES-supplemented'' group ($p = 0.6673$). The male to female sex distribution was 10:4 and 7:5 for the ''crystalloid only'' and the ''HES-supplemented'' group respectively.

The median TBSA burn was 23.5% for the ''crystalloid only'' and 32.5% for the ''HES-supplemented'' group ($p = 0.0673$, Mann–Whitney U test). There was, however, a significant difference between the proportion of full thickness burn (FTB) between the two fluid regime groups. The median (95%CI) %FTB for the ''crystalloid only'' and ''HES-supplemented'' group was 9% (5–14) and 18.5% (11–28) respectively ($p = 0.020$). There was no statistically significant difference between the two groups in terms of median delay from injury to hospital admission, median base excess or serum creatinine on presentation, mean hourly urine output, heart rate or mean arterial pressure (Table 1).

Mean serum creatinine at 24 h post-injury was lower in the ''crystalloid group'', 74 μmol/L versus 82 μmol/L, but the difference was not statistically significant ($p = 0.3303$, unpaired Student t-test) (Table 1).

None of the patients required renal replacement therapy.

3.1. *Fluid resuscitation volume received in the first 24 h*

There was no difference in the median total volume of resuscitation fluid received, in the first 24 h post-injury, between the ''crystalloid only'' and the ''HES-supplemented'' group ($p = 0.9798$, Mann–Whitney U test). Median total volume of fluid infused per %TBSA burn, however, was significantly different between the two groups, 307 ml/% for the ''crystalloid only'' and 263 ml/% for the ''HES-supplemented'' group ($p = 0.0234$). The median volume of fluid received, in the first 24 h post-injury, per % TBSA burn, per body weight was 4.2 ml/kg/% for the ''crystalloid only'' and 3.8 ml/kg/% for the ''HES-supplemented'' group ($p = 0.2740$, Mann–Whitney U test) (Table 2).

3.2. *Effect of different fluid regimes on body weight*

Body weight gain within the first 24 h after injury was compared between the two fluid regime groups and found to be significantly different ($p = 0.0039$, Mann–Whitney U test). The median weight gain was 2.5 kg and 1. 4 kg for the ''crystalloid only'' and the ''HES-supplemented'' group respectively. This difference was maintained when looking at weight gain per %TBSA within the first 24 h; the median weight gain/

Table 1 – Patient demographic and vital signs data.

	Crystalloid only $n = 14$	HES-supplemented $n = 12$	p
Mean (SD) age	42.4 (±23.5)	40.8 (±20.1)	0.6673
Male: female	10:4	7:5	–
Median (95%CI) %TBSA burn	23.5 (18–32)	32.5 (22–50)	0.0673
Median (95%CI) % FTB	9 (5–14)	18.5 (11–28)	0.0202
Inhalation injury	4	4	–
Mortality in hospital	2	2	–
Median time interval (95%CI) from injury to hospital admission (h)	3 (2–4)	2.5 (1.5–3.5)	0.2311
Median (95%CI) base excess on admission	−1.1 (−4.6 to 2.4)	−2.8 (−6 to −0.9)	0.2678
Mean serum creatinine (SD) on admission (μmol/L)	90 (±10)	92 (±13)	0.8500
Mean serum creatinine (SD) at 24 h post-injury (μmol/L)	82 (±9.5)	74 (±59–90)	0.3303
Mean hourly urine output (SD) (ml/kg/h)	1.3 (±0.35)	1.15 (±0.2)	0.2039
Median (95%CI) MAP (mm Hg)	86 (75–90)	82 (69–91)	0.6646
Median (95%CI) HR (beats/min)	84 (69–109)	99 (82–114)	0.2661

SD = standard deviation, TBSA = total body surface area, FTB = full thickness burn, CI = confidence interval, MAP = mean arterial pressure, HR = heart rate.

Table 2 – Resuscitation fluid data.

	Crystalloid only $n = 14$	Colloid-supplemented $n = 12$	p
Median data for first 24 h post-burn			
Volume of fluid infused (ml)	8450	8650	0.9798
Volume infused/%TBSA (ml)	307	263	0.0234
Volume infused/%TBSA/patient weight (ml/kg)	4.2	3.8	0.2740
Volume infused − volume predicted (range)	+545 (−835 to +3175)	−391 (−1084 to +2210)	0.2972
Crystalloid volume (ml)	8450	7306	–
HES volume (ml)	0	1585	–
Weight gain (kg)	2.5	1.4	0.0039
Weight gain/%TBSA	0.078	0.046	0.0037
Weight gain/%FTB	0.2	0.1	0.0055

TBSA = total body surface area, FTB = full thickness burn.

%TBSA was 0.078 kg and 0.046 kg for the ''crystalloid only'' and the ''HES-supplemented'' group respectively ($p = 0.0037$). The significance also applied to weight gain per % FTB; 0.2 kg versus 0.1 kg in each group respectively ($p = 0.055$) (Table 2).

3.3. *Effect of different fluid regimes on base excess at 12 h*

Base excess at 12 h after injury was also compared between the two fluid regime groups and the values were found to be normally distributed. The mean base excess was −2.9 mmol/L (95% CI −4.92 to −0.93) and −1 mmol/L (95% CI −2.48 to 0.43) for the ''crystalloid only'' and the ''HES-supplemented'' group respectively, but the difference did not reach statistical significance ($p = 0.0871$, independent samples t-test).

3.4. *Effect of different fluid regimes on respiratory function*

Oxygen saturation (%$SatO_2$) corrected for inspired oxygen % ($SatO_2/FiO_2$ ratio) during the first 48 h post-injury was compared between the two fluid regime groups and the values were found to be normally distributed. The monitoring duration was divided into six 8-h periods as shown in Table 3. The difference between the two groups was only statistically significant between 3 h and 8 h after burn, oxygenation being better in the ''crystalloid only'' group ($p = 0.00328$, independent samples t-test). There was no difference in oxygenation between the two groups beyond 8 h post-burn.

3.5. *Effect of different fluid regimes on serum C-reactive protein*

There was a statistically significant difference between the two groups in terms of serum C-reactive protein (CRP) concentration at 48 h post-injury. The median CRP was 210 mg/L and 128 mg/L for the ''crystalloid only'' and the ''HES-supplemented'' groups respectively ($p < 0.0001$ Mann–Whitney U test) (Table 4).

3.6. *Effect of different fluid regimes on urine ACR*

Albumin–creatinine ratio (ACR) which is an indicator of endothelial dysfunction was compared between the two groups. There was no demonstrable difference between the two groups in ACR at 6, 12 or 24 h or in the duration of elevated ACR. When the ACR at 12 h was, however, corrected for %TBSA burn, to account for the discrepancy in median burn size between the two fluid regime groups, the difference became statistically significant; the ACR/%TBSA at 12 h was 0.04 mg/mmol and 0.02 mg/mmol for the ''crystalloid only'' and the

Table 3 – Respiratory function data.

Mean (SD) $\%SatO_2/FiO_2$ ratio during post-burn periods	Crystalloid only $n = 14$	HES-supplemented $n = 12$	p
3–8 h	387 (114.5)	283 (61.8)	0.0328
9–16 h	371 (64.8)	335 (94.3)	0.3188
17–24 h	377 (70.6)	348 (86.1)	0.4060
25–32 h	381 (71.4)	341 (86.8)	0.2638
33–40 h	385 (83.6)	340 (85.8)	0.3119
41–48 h	375 (102.3)	354 (100.7)	0.6903

SD = standard deviation, $\%SatO_2$ = oxygen saturation, FiO_2 = inspired oxygen.

Table 4 – Inflammatory marker data.

	Crystalloid only $n = 14$	Colloid-supplemented $n = 12$	p
Median (95%CI) serum CRP at 48 h (mg/L)	210 (167–257)	128 (74–145)	0.0001
ACR at 6 h (mg/mmol)	2 (0.4–6.4)	2.6 (0.5–24.5)	0.4319
ACR at 12 h (mg/mmol)	1.3	1	0.4025
12 h ACR/%TBSA	0.04	0.02	0.0310
12 h ACR/%FTB	0.14	0.05	0.0080

CI = confidence interval, CRP = C-reactive protein, ACR = albumin–creatinine ratio, TBSA = total body surface area, FTB = full thickness burn.

''HES-supplemented'' groups respectively ($p = 0.0310$, Mann–Whitney U test). The same applied to ACR correction for % FTB ($p = 0.0080$) (Table 4).

4. Discussion

The Parkland formula under-estimates fluid requirement in up to 50% of cases [8–11]. Crystalloid ''fluid creep'' to achieve optimal haemodynamic parameters can lead to interstitial oedema with associated morbidity. Centres that rely on crystalloid resuscitation alone have been reporting an increase in limb and abdominal compartment syndromes [19]. The revelation in the early 1950s that burn fluid loss was plasma, suggested that replacing like with like may be beneficial. Human albumin, the main plasma substitute available at the time, was recommended once the capillary integrity had been restored, to prevent protein extravasation into the interstitium and oedema [20]. Its small molecular size, cost and associated infection risk have led to major developments in synthetic alternatives including starches.

The refinement in the latter group of colloids has created a shift from the early high-molecular-weight, highly substituted starch-based colloids, like Hespan, to ones which are rapidly cleared from the circulation. They do not accumulate in tissues, have a minimal effect on clotting and possibly even offer renal protection [21,22].

The mean TBSA burn size in the present study was modest at 27% due to the withdrawal of three patients that required treatment outside protocol. The three patients that were excluded for receiving HES for haemodynamic stabilisation (while in the ''crystalloid only'' arm) had a mean TBSA of 60%.

There was no difference in mortality between the two groups. Due to the small number of patients, however, it is not possible to draw any significant conclusions using mortality as an outcome measure. The non-survivors were considerably ''sicker'' patients with a poor prognosis. All had suffered severe inhalation injury and had a mean TBSA burn of 61%.

There was no difference in burn size or inhalation injury between the two groups, but percentage of full thickness burn was significantly greater in the ''HES-supplemented'' group. As prognosis weight of full thickness burn area is considered superior to that of the total burn area, patients in the ''HES-supplemented'' group may have been at a relative disadvantage prior to randomisation.

The present study shows that HES-supplemented resuscitation is associated with less fluid requirement and less weight gain. The ''crystalloid only'' group required a median of 545 ml in addition to the Parkland formula predicted volume for the first 24 h, whereas the ''HES-supplemented'' group received a median of 391 ml less. This supports the finding from Professor Kramer's experiments in 1996 that 6% hetastarch halved burns fluid volume resuscitation in sheep [23]. Another recent clinical study also showed significant fluid saving and less weight gain following hydroxyethylstarch-augmented burn resuscitation [24].

The clinical relevance of minimising resuscitation fluid volume required to achieve adequate perfusion is to minimise organ dysfunction, which is proportional to the volume of fluid extravasation [10]. Fluid retention in the first 48 h post-burn is also known to correlate well with mortality.

The difference in fluid requirement between the two groups can be explained by the fact that HES remains intravascular for longer. This was reflected by the dilutional effect recorded in serum albumin concentration post-injury (Table 1). The difference in albumin dilution between the two groups was maintained at 48 h after injury and resuscitation.

Evidence from trauma and surgery research suggests that hydroxyethylstarches also offer pulmonary, renal and splanchnic protection [17,18]. In terms of respiratory function the only period during which a significant difference was

detected between the two groups was between 3 h and 8 h post-burn. As the infusion of 6% HES did not start until after 4 h post-injury, it is unlikely that this had time to affect respiratory function in the first 8-h period. The fact that oxygenation appeared poorer in the ''HES-supplemented'' group is in line with the significantly worse baseline acidosis and % full thickness burn in this group. There was no difference in oxygenation between the two groups between 8 h and 48 h post-burn which supports the lack of deleterious effect of this type of colloid on pulmonary function and gas exchange. PaO_2/FiO_2 ratio would have been a more accepted indicator of ventilation, but hourly arterial blood gas analysis was not practical in non-ventilated patients. A regression analysis comparing PaO_2/FiO_2 ratio to $SatO_2/FiO_2$ ratio at 71 time points showed a good correlation at 95% confidence and prediction interval. There was no difference in serum creatinine between the two groups at 24 h after injury. Hydroxyethylstarches administered with adequate crystalloid within the daily allowance limits, may even offer renal protection [25].

Hydroxyethylstarches have more to offer than their volume-expanding properties; they are known to modulate the inflammatory response [12–14].

The current study revealed a significantly lower serum C-reactive protein (CRP) level at 48 h and microalbuminuria at 12 h (when corrected for burn size) in patients receiving HES-supplemented resuscitation. As CRP is a protein and dilution of serum albumin was also demonstrated, one would argue that the lower CRP level may be purely dilutional. The decrease, however, in the serum CRP level at 48 h was four times higher than the drop in serum albumin.

The difference in base excess at 12 h after injury between the two groups did not reach statistical significance ($p = 0.0871$) likely due to the small number of patients. The ''crystalloid only'' group, however, showed worsening of acidosis between admission and 12 h post-injury, as opposed to the tissue perfusion recovery seen in the ''HES-supplemented'' group. Since the correction of acidosis after burn is known to be a predictor of outcome, it would be interesting to explore whether or not hydroxyethylstarch supplementation has the potential of affecting prognosis favourably.

In conclusion, HES-supplemented burns resuscitation allows for smaller fluid volume requirement and less tissue oedema, in the first 24 h. This along with a significantly lower burn size-adjusted capillary leak at 12 h and a dampened inflammatory response at 48 h after injury, suggest that the potential benefits of hydroxyethylstarch in the management of burns patients ought to be explored further. There was no evidence of renal dysfunction with the use of HES in burns patients. A larger multi-centre prospective study to consolidate the above findings and assess further outcomes such as cardiovascular performance, patient ventilation, intra-abdominal hypertension and mortality would offer first class evidence to help optimise burn victims' fluid resuscitation further.

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Conflict of interest

The UHB Clinical Biochemistry Department has received two research grants from Byer Diagnostics, Germany, for the partial funding of projects not related to the above study. The Eleganza ITU Weighing System was provided on trial by Pegasus LTD., Waterlooville, Hants, UK.

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