Safety, Pharmacodynamics, and Efficacy of High- Versus Low-Dose Ascorbic Acid in Severely Burned Adults

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In sepsis and burns, ascorbic acid (AA) is hypothesized advantageous during volume resuscitation. There is uncertainty regarding its safety and dosing. This study evaluated high dose AA (HDAA: 66 mg/kg/h for 24 hours) versus low dose AA (LDAA: 3.5 g/days) administration during the first 24 hours in severely burned adults. We conducted a retrospective study comparing fluid administration before and after switching from low dose to HDAA in severely burned adults. A total of 38 adults with burns >20% TBSA, who received either HDAA or LDAA were included in this retrospective study. AA serum concentrations were quantified at 0, 24, and 72 hours postburn. HDAA impact on hemodynamics, acid–base homeostasis, acute kidney injury, vasopressor use, resuscitation fluid requirement, urinary output, and the incidence of adverse effects was evaluated; secondary clinical outcomes were analyzed. AA plasma levels were 10-fold elevated in the LDAA and 150-fold elevated in the HDAA group at 24 hours and decreased in both groups afterwards. HDAA was not associated with a significantly increased risk of any complications. A significant reduction in colloid fluid requirements was noted (LDAA: 947 ± 1722 ml/24 hours vs HDAA: 278 ± 667 ml/24 hours, $P = 0.029$). Other hemodynamic and resuscitation measures, as well as secondary clinical outcomes were comparable between groups. HDAA was associated with higher AA levels and lower volumes of colloids in adults with severe burns. The rate of adverse events was not significantly higher in patients treated with HDAA. Future studies should consider prolonged administration of AA.

Severe thermal trauma induces a complex systemic response of hyperinflammation and hypermetabolism,[1,2] which entails intravascular volume depletion due to capillary leak,[3,4] immunodeficiency with increased risk for infection and sepsis,[5,6] deficiencies of various macro- and micronutrients,[7,8] and a surge of deleterious free radicals due to relative tissue hypoxemia and impaired antioxidant mechanisms.[9] High volume fluid resuscitation,[10] anti-infective, and immunomodulatory therapy,[11,12] as well as anti-inflammatory and anabolic interventions to modify the hypermetabolic response[13,14] have been introduced to burn care with significant improvements in clinical outcomes and overall survival.[15] Ascorbic acid (AA) is an essential, water-soluble micronutrient, that serves as an electron donor in multiple enzymatic reactions, including the synthesis of endogenous catecholamines and collagen.[16] Recent evidence suggests systemic depletion of AA in critically ill patients on the one hand and positive effects of AA administration during acute septic shock on vasopressor (noradrenaline) use and duration, as well as overall mortality.[17] Similarly, in burn care, administration of high dose AA during the acute phase of burn shock resuscitation has been shown in animal models and clinical studies to reduce fluid requirements during resuscitation, potentially counteracting negative influences of fluid overload.[18–20] However, there remains uncertainty regarding the dosing and safety of AA in burns: in a recent retrospective review, Lin et al raised concerns that AA administered at a dose of 66 mg/kg/h during initial resuscitation of severely burned adults may not improve fluid requirements or clinical outcomes and might increase the risk for acute kidney injury (AKI) and subsequent renal failure.[21] The aim of this retrospective analysis is to compare the safety and pharmacodynamics of high- versus low-dose administration of AA during the first 24 hours of acute burn shock resuscitation in severely burned adults.

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Conflict of interest statement. The authors declare that there are no financial and personal relationships with other entities or organizations that could potentially and inappropriately influence (bias) their work and conclusions.

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doi:10.1093/jbcr/iraa041

METHODS

Approval

This study was approved by the Ethics Committee of Rheinland-Pfalz, the assigned study number is 2019-14562.

Study Design and Patient Inclusion

On February 1, 2017 our burn center changed its standard of care regarding dosing of AA on admission of adults with severe thermal trauma. Severely burned patients admitted to

our burn center until January 31, 2017 received low dose AA (LDAA = 3.5 g) upon admission, whereas patients admitted from February 1, 2017 on received HDAA (66 mg/kg/h for 24 hours). In total, 38 patients with burns covering extent of more than 20% of total body surface area (% TBSA) that were admitted between July 2016 and January 2018 were included in this retrospective before-and-after-study. Patients were assigned to the pre-protocol-change group (n = 19) or the post-protocol-change group (n = 19) based on their date of admission. Those admitted July 1, 2016 through January 31, 2017 were considered part of the pre-change group and were treated with LDAA, whereas the following 19 patients admitted after February 1, 2017 received HDAA. Only patients admitted immediately after burn trauma were included in this trial, so that the AA treatment was started simultaneously with volume resuscitation therapy, within 3–4 hours after trauma. All patients were of legal age (>18 years) and did not suffer from an iron storage disease like hemochromatosis or thalassemia.

Fluid Resuscitation

Fluid resuscitation was initiated preclinically and continued upon admission with crystalloid fluids according to the modified Brooke-formula (2 ml × kg body weight × % TBSA per 24 hours). The infusion rate was reevaluated every 2 hours during the first 48 hours postburn: measured through PiCCO, target global enddiastolic index (GEDI) was ≥480 ml/m^2, target cardiac index (CI) was ≥2.5 l/min/m^2, target hourly urinary output (UO) was ≥ 0.5 ml/kg and target mean arterial pressure (MAP) was ≥ 70 mm Hg. Failure to meet one of the targets triggered a 20% increase in hourly volume input, over-accomplishment (GEDI ≥ 640 ml/m^2, UO ≥ 1 ml/kg, triggered a stepwise reduction in infusion rate.[22] Colloid fluids were administered earliest after the first 8 hours of resuscitation substituting up to one-third of total crystalloid volume based on the algorithm if target criteria (GEDI, CI, MAP, and urine output) could not be met with several 20% increases in hourly resuscitation volume as assessed every 2 hours. In conjunction with fluid infusion rates, use of catecholamines was considered if targets of CI (dobutamine) or MAP (norepinephrine) were not met.

Administration of AA and Safety Monitoring

All patients included in the study received AA intravenously directly upon admission. Patients in the LDAA group received 3.5 g as a single infusion (Vitamin C-Rotexmedica 500 mg/5 ml, Rotexmedica GmbH Arzneimittelwerk, Trittau, Germany), whereas subjects in the HDAA group were infused continuously over 24 hours with 66 mg/kg per hour intravenously (Pascorbin® 7.5 g/50 ml, Pascoe, Giessen, Germany). Both products contained besides AA only sodium bicarbonate and sterile isotonic water for injection (Fresenius KABI, Bad Homburg, Germany) as the carrier solution. Pascoe is the only company supplying high-dose-infusion AA in Europe so that we had to change the producer. The extra fluid administered to the HDAA group for continuous AA infusion was included in the 24-hour crystalloid intake calculations. Prior to the adjustment of the AA dosing it was agreed to stop HDAA treatment immediately if patients had hypotension (fall of mean arterial blood pressure of >20 mm Hg, or systolic blood pressure < 90 mm Hg), hypertension (systolic blood pressure > 160 mm Hg) tachycardia (increasing heart rate of > 20 beats per minute), hypernatremia (>145 mmol/l), nausea or vomiting upon AA infusion.

Study Variables

Patient data for age, sex, height, weight, abbreviated burn severity index (ABSI), Charlson Comobridity Index (CCI), % TBSA, % full-thickness TBSA, inhalation injury (IHT), total 24-hour resuscitation fluid requirement, urine output, need of vasopressors (noradrenaline, VASO), ventilator days (VENT), incidence of pneumonia, renal replacement therapy (RRT), number of surgeries needed, total hospital length of stay for survivors (LOS) and mortality were retrospectively collected by chart-review. Incidence and severity of AKI were calculated based on the AKIN criteria.

Heart rate and MAP were monitored continuously with a multichannel hemodynamic monitor (infinity c700 workstation with m 540 docking station (DRÄGER, Lübeck, Germany). Moreover, hemodynamic parameters were monitored based on transpulmonary thermodilution[22] by Pulse Contour Cardiac Output (PiCCO) every 2–6 hours in case that the system was placed (PiCCO, Pulsion Medical Systems SE, Feldkirchen, Germany). Venous and arterial blood samples were drawn upon admission, as well as 24 and 72 hours after admission and analyzed automatically for pH, acid/base balance, base deficit, hematocrit, leucocytes, C-Reactive Protein (CRP), creatinine level, and serum albumin. All data were analyzed after collection by chart review.

Plasma AA Measurements

As part of our quality control standard when establishing the HDAA-protocol at our center, AA levels were quantified in EDTA blood samples drawn at admission, as well as 24 and 72 hours after admission in all patients. Plasma was stored after centrifugation in a protective AA tube in the dark at −80°C prior to analysis by liquid chromatography–mass spectrometry (LC-MS) (SCIEX QTRAP® 5500, Framingham, USA).

Statistical Analysis

Data are presented as mean values ± standard deviation (SD), medians, and ranges. Results were compared using Student's unpaired t-test, Mann–Whitney U-test, or one-way ANOVA, depending on normal distribution of datasets assessed by Shapiro–Wilk test. Paired repeated parametric measurements were analyzed with two-way ANOVA and Tukey's correction for multiple comparisons. Contingencies were compared using Fisher's exact test. Statistical analyses were performed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla CA). Statistical significance was accepted at $P < 0.05$.

RESULTS

Nineteen patients were included in each of the two groups, which were comparable for patient age (LDAA: 49 [18–84] years vs HDAA: 47 [22–81] years, $P = 0.582$) and sex distribution (6 female and 13 male patients in each group, $P = 0.999$). There were no significant differences in BMI (LDAA: 31.0 ± 6.8 vs HDAA: 27.4 ± 6.7, $P = 0.080$), CCI (median score

LDAA: 1 [0–8] vs HDAA: 0 [0–6], P = 0.215), ABSI score (median score LDAA: 7 [4–12] vs HDAA: 7 [5–12], P = 0.881), % TBSA (LDAA: 34.5 ± 18.2% vs HDAA: 35.5 ± 16.1%, P = 0.952), mean % full-thickness TBSA (LDAA: 9.1 ± 18.8% vs HDAA: 7.9 ± 12.6%, P = 0.490), or incidence of IHT (LDAA: n = 3; 15.8% vs HDAA: n = 4; 21.0%, P > 0.999) between the LD and HD group (Table 1).

Plasma AA levels at admission were at 1.01 ± 1.52 mg/l (5.73 ± 8.63 µmol/l) in the LD group and 2.94 ± 3.0 mg/l (16.69 ± 17.03) in the HD group (P > 0.05). Administration of AA elevated plasma ascorbic levels in both groups; in the LD group the average AA plasma concentration increased approximately 9-fold to 8.74 ± 18.26 mg/l (49.63 ± 103.68 µmol/l) 24 hours after admission while the AA concentration in the HD group increased 150-fold to 458.21 ± 241.95 mg/l (458.21 ± 382.12). Afterwards, AA plasma levels decreased in both groups when measured 72 hours after admission to an average concentration of 5.69 ± 10.77 mg/l (32.31 µmol/l ± 61.15 µmol/l) in the LD and 174.91 ± 241.95 mg/l (993.13 ± 1373.78 µmol/l) in the HD group. AA levels were significantly higher 24 and 72 hours after admission when HDAA was administered instead of LDAA (24 hours: P < 0.01 and 72 hours: P < 0.05) (Table 2 and Figure 1A). HDAA infusion was not associated with increased risk of AKI, renal failure, disturbances in acid–base homeostasis or any other investigated measure of adverse events as described in Tables 3 and 4.

Overall resuscitation volumes during the first 24 hours were trending lower in the HD group than with LDAA, without reaching statistical significance (LDAA: 8169 ± 7009 ml/24 h vs HDAA: 6188 ± 3556 ml/24 h, P = 0.596; Table 3 and Figure 1B). Colloid fluid administration was significantly lower when HDAA was administered (LDAA: 947 ± 1722 ml/24h vs HDAA: 278 ± 667 ml/24 h, P = 0.029; Table 3 and Figure 1C). Vasopressor use also trended lower in the HD than in the LD group during the first 24 hours (LDAA: 42.1% vs HDAA 26.3%, P = 0.495) as well as during the first 3 days (LDAA: 52.6% vs HDAA 26.3%, P = 0.184) without reaching statistical significance. Overall resuscitation volume on days 2 and 3 after admission tended to be slightly higher in the HD than in the LD group, but the difference was not statistically significant (LDAA: 7240 ± 5189 ml/48 h vs HDAA: 7913 ± 6042 ml/48 h, P = 0.818). Acid–base balance stayed almost equal in both groups at any time of measurement (Table 3), and no differences in lactate levels were observed between groups.

Crude total urine output in the first 24 hours post admission was higher in the HD group (24-hour total urine output: LDAA: 1756 ± 1340 ml/24 h vs HDAA: 2468 ± 1441 ml/24 h, P = 0.032); likewise, urine output normalized to body weight was higher (LDAA: 0.82 ± 0.56 ml/kg/h vs HDAA: 1.24 ± 0.7 ml/kg/h, P = 0.013). On days 2 and 3 after admission total urine output decreased more in the HD than in the LD group, but results did not differ significantly (24–72-hours total urine output: LDAA: 4120 ± 2165 ml/48 h vs HDAA: 3331 ± 1427 ml/48 h, P = 0.153). Mean plasma creatinine levels were normal in both groups at admission and increased in the first 24 hours after admission without being significantly different between the groups. About 72 hours after admission, creatinine levels decreased again in both groups (Table 4).

The number of ventilator days trended lower in the LDAA group without reaching statistical significance (LDAA: 10.1 ± 20.9 days vs HDAA: 19.5 ± 26.0 days, P = 0.064). Pneumonia during the first 7 days postburn trauma occurred twice in both groups (10.5% each group, P = 1). RRT was necessary for two patients in each group during the first 72 hours after admission (10.5%, P = 1), and a total of three patients of the LD group and four patients of the HD group required renal hemodialysis during their entire hospital stay (LDAA: 15.8% vs HDAA: 21.0%, P = 1). The number of surgeries performed in both groups was similar (LDAA: 4.0 ± 3.7 vs HDAA: 4.7 ± 3.7 P = 0.854). There were no significant differences in LOS (LDAA: 58 ± 46 days vs HDAA: 39 ± 33 days, P = 0.08) or

Table 1. Patient demographic and clinical outcomes

Variable	LDAA (n = 19)	HDAA (n = 19)	P	Mean Difference (95% CI)
Age (years)	49 ± 17.9	47 ± 18.8	0.582	−1.27 (−13.5 to 11)
Sex (female:male)	6:13	6:13	0.999	N/A
BMI	31.0 ± 6.8	27.4 ± 6.7	0.080	−3.7 (−8 to 0.8)
CCI	1 (0 to 8)	0 (0 to 6)	0.215	N/A
ABSI	7 (4 to 12)	7 (5 to 12)	0.880	N/A
TBSA	34.5 ± 18.2	35.5 ± 16.1	0.952	−1 (−13 to 11)
% full thickness TBSA	9.1 ± 18.8	7.9 ± 12.6	0.490	−1 (−12 to 9)
IHT (%)	15.8	21.0	0.999	N/A
Pneumonia (%)	10.5	10.5	0.999	N/A
VENT (d)	10.1 ± 20.9	19.5 ± 26.0	0.064	9.4 (−6.1 to 25)
RRT during acute care (%)	15.8	21.0	0.999	N/A
RRT at discharge (%)	5.2	5.2	0.999	
No. of surgeries	4 ± 3.7	4.7 ± 3.7	0.854	0.7 (−1.8 to 3.1)
LOS (d)	58 ± 46	39 ± 33	0.08	−19 (−48 to 10.1)
Mortality (%)	10.5	26.3	0.405	N/A

BMI, body mass index; *CCI*, Charlson Comorbidity Index; *ABSI*, Abbreviated Burn Severity Index; *TBSA*, percentage of total body surface area of burn injury; *3° TBSA*, percentage of third degree total body surface area of burn injury; *IHT*, inhalation trauma; VENT, ventilator days; *RRT*, renal replacement therapy; *No. of Surgeries*, number of burn associated surgeries; *LOS*, hospital length of stay; *d*, days; *CI*, confidence interval.
All values are mean ± standard deviation, median values and range or mean differences with a 95% confidence interval.

Table 2. AA concentrations in serum during 72 hours after burn injury following continuous LDAA and HDAA administration for 24 hours

	LDAA (3.5 g/d)				HDAA (66 mg/kg/h for 24h)					Mean Difference 95% CI	
Timepoint	mg/l	SD	µmol/l	SD	mg/l	SD	µmol/l	SD	*P*	mg/l	µmol/l
0 h	1.01	1.52	5.73	8.63	2.94	3.00	16.69	17.03	0.0554	−1.9 (−3.9 to 0.04)	−109.6 (−221.1 to 2.0)
24 h	8.74	18.26	49.63	103.68	458.21	382.12	2601.69	2169.66	0.0002	−449.5 (−680.3 to −218.6)	−2525.569 (−3838.674 to −1212.465)
72 h	5.69	10.77	32.31	61.15	174.91	241.95	993.13	1373.78	0.0258	−169.2 (−320 to −18.9)	−9086 (−1717.266 to −906)

LDAA, low dose ascorbic acid; *HDAA*, high dose ascorbic acid; *SD*, standard deviation; *CI*, confidence interval.
All values are mean ± standard deviation.

mortality rate (LDAA: $n = 2$; 10.5% vs HDAA: $n = 5$; 26.3%, $P = 0.405$; Table 1).

DISCUSSION

In this study, we provide dose-dependent AA plasma concentrations for the first 72 hours after burn injury. We did not find the use of HDAA to be associated with increased risk of AKI, renal failure, disturbances in acid–base homeostasis, or any other investigated measure of adverse events. A reduction in colloid fluid requirements was noted, as well as trends towards reduced crystalloid fluid and vasopressor requirements during the first 24 hours postburn.

There is mounting evidence from various experimental and clinical studies in acute sepsis and burn care for positive effects of AA during clinical states of volume resuscitation caused by systemic hyperinflammation, which is a common trait between sepsis and burns.[17–19] It is understood, that relative tissue hypoxemia and reperfusion induce an acute surge in systemic production of oxygen-free radicals (OFR) through xanthine oxidase[9]; OFR in turn damage cellular DNA directly,[23] aggravate intravascular hypovolemia by increasing peripheral vascular permeability,[24] and negatively impact the structure and function of the heart, kidney, and lung directly.[9,25,26] The OFR-scavenging properties of AA, together with the known systemic depletion of AA following septic shock and acute severe burn injury are at the core of the rationale to administer the agent during resuscitation. In summary, this evidence has led us to change our practice from LDAA to HDAA in the acute setting, while all other parameters of burn care remained the same during the before-and-after periods. Our investigation with 38 patients (19 LDAA and 19 HDAA) is the largest retrospective study to investigate the safety of LDAA and HDAA in the resuscitation of severely burned adults. The two study groups were similar with respect to burn severity as per TBSA% affected and the occurrence of IHT, and were comparable in terms of age and sex distribution.

To date, the optimal plasma concentration for AA, in order to balance efficacy and safety, is unknown and argued over both in sepsis and in burn care. Our data show that, at baseline postburn injury, AA concentrations in plasma are lower than normal in both groups.[27,28] This finding is in concordance with a phase I safety trial of AA in sepsis that found patients to exhibit similarly reduced AA levels at study entry (Figure 1A overlay,[27]). In our study, HDAA administration at the dose that Tanaka et al used in the initial clinical description of the procedure (66 mg/kg/h continuously for 24 hours) elevated the average concentration of AA in patient plasma 150-fold to 2600 µmol/l after 24 hours, while the low dose of 3.5 g/d merely elevated plasma levels 10-fold. Fowler et al described an increase of serum AA to over 3000 µmol/l on day 4 which corresponds to a 175-fold increase from baseline.[27] They achieved this result with the administration of 200 mg/kg/d for 4 days which amounts to a cumulative dose of 64 g. A comparable HDAA subject in this study would have received 126 g AA within 24 hours per our dosing regimen. One possible explanation for this discrepancy might be the more severely disturbed fluid balance in acute thermal trauma, leading to higher resuscitation volumes and increased dilution effects due to increased capillary permeability with subsequent

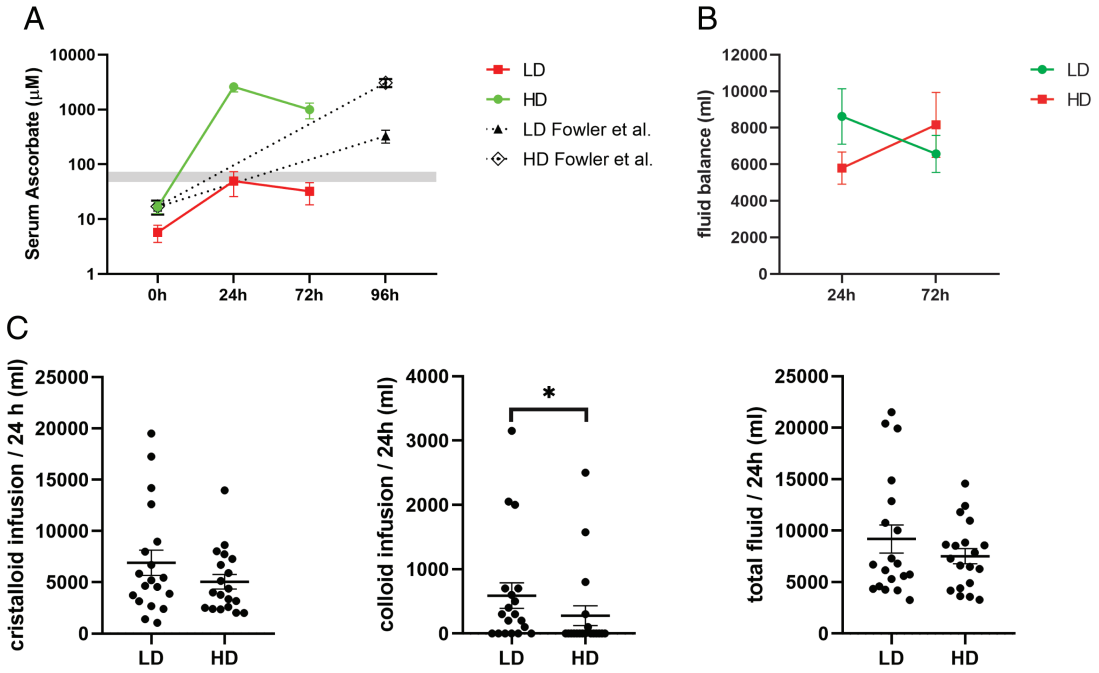

Figure 1. A. Serum concentrations of AA at baseline, 24 and 72 hours postburn, upon HD or LD administration. Data from Fowler et al.[27] superimposed for comparison, who administered 200 mg/kg per day (HD) or 50 mg/kg per day for 4 days. Grey area indicates normal serum concentration of AA. B. Fluid balance during burn shock resuscitation at baseline, 24 and 72 hours postburn. C. Crystalloid, colloid, and total fluid infusion during 24 hours continuous administration of AA (HD) or after one-time AA administration (LD). *AA*, ascorbic acid; *HD*, high dose; *LD*, low dose.

Table 3. Burn shock resuscitation volumes, acid–base balance and vasopressor use

Variable	LDAA (n = 19)	HDAA (n = 19)	P	Mean Difference 95% CI
24-h ml/kg/% TBSA	2.23 ± 1.6 1.49 (1.45 to 3.01)	2.06 ± 0.85 1.77 (1.65 to 2.47)	0.66	0.17 (−0.67 to 1.01)
24-h crystalloid fluid (ml)	6907 ± 5321 5325 (4732 to 9820)	5691 ± 3017 4003 (3566 to 6540)	0.818	1216 (−1630 to 4062)
24-h colloid fluid (ml)	947 ± 1722 300 (171 to 1008)	278 ± 667 0 (43 to 599)	**0.029**	669 (190 to 1528)
24-h total fluid (ml)	8169 ± 7009 6750 (6698 to 12.228)	6188 ± 3556 7288 (5958 to 9081)	0.596	1970 (−1687 to 5627)
24–72-h total fluid (ml)	7240 ± 5189 6380 (4739 to 9741)	7913 ± 6042 6144 (5001 to 1010.825)	0.818	673 (−3033 to 4379)
24-h pH	7.35 ± 0.05 7.36 (7.32 to 7.37)	7.37 ± 0.07 7.38 (7.34 to 7.41)	0.318	0.02 (−0.02 to 0.06)
24–72-h pH	7.39 ± 0.1 7.37 (7.34 to 7.44)	7.4 ± 0.06 7.4 (7.37 to 7.43)	0.718	0.01 (−0.044 to 0.064)
24-h VASO use (%)	42.1	26.3	0.495	N/A
24–72-h VASO use (%)	52.6	26.3	0.184	N/A

% TBSA, percentage of total body surface area of burn injury; *VASO*, vasopressor; *N/A*, not applicable.
All values are mean ± standard deviation or median and range.

loss of fluid and active low-molecular agents such as AA into the interstitial space. It may therefore be necessary to administer higher doses of AA during burn shock resuscitation than to patients in septic shock. Clearly, large prospective dosing trials are needed to determine optimal dosing of AA to achieve therapeutic serum concentrations. It would further be of great interest to objectify what a therapeutic serum concentration actually is: one potential modality of doing so could be the longitudinal monitoring of systemic oxidation–reduction potential (ORP), which has been used to differentiate trauma severity and extent of inflammation and is currently evaluated for other etiologies outside of multi-trauma.[29]

Safety of the administered HDAA was a primary endpoint of this study. No continuous AA administration had to be

Table 4. Renal function: urine output, serum measurement of creatinine, and RRT

Variable	LDAA (*n* = 19)	HDAA (*n* = 19)	*P*	Mean difference 95% CI
24-h total urine output (ml)	1756 ± 1340	2468 ± 1441	0.032	712 (−195 to 1619)
24-h hourly urine output (ml/kg/h)	0.82 ± 0.56	1.24 ± 0.7	0.013	0.42 (−0.003 to 0.837)
24–72-h total urine output (ml)	4120 ± 2165	3331 ± 1427	0.153	789 (−417 to 1995)
Admission Crea (mg/dl)	1.14 ± 0.64	0.99 ± 0.34	0.373	0.15 (−0.187 to 0.487)
24-h Crea (mg/dl)	1.67 ± 1.18	1.85 ± 0.9	0.603	0.18 (−0.51 to 0.87)
72-h Crea (mg/dl)	1.32 ± 1.23	1.27 ± 0.76	0.765	0.05 (−0.62 to 0.72)
72-h RRT (%)	10.5	10.5	0.999	N/A
Total RRT (%)	15.8	21.0	0.999	N/A
AKI (AKIN) stage: *n* (%)			0.47	N/A
0	5 (28)	4 (21)		
1	5 (28)	7 (27)		
2	7 (39)	5 (26)		
3	1 (6)	3 (15)		

Crea, serum creatinine; *RRT*, renal replacement therapy; *AKI*, acute kidney injury; *N/A*, not applicable.
All values are mean ± standard deviation.

halted due to study adverse effects as described above. This is in concordance with the prospective trials of Tanaka et al and Fowler et al who reported similar results with their comparable or cumulatively lower doses of AA.[19,27] One main concern raised in the retrospective review by Lin et al was a trend towards increased risk of AKI and renal failure requiring dialysis in their collective of severely burned adults.[21] We found no increased incidence of AKI, percentage of patients with abnormally low diuresis, or need for RRT. We acknowledge that this absence of evidence is not conclusive and that our trial might have been underpowered to detect certain complications. On the other hand, renal complications following severe thermal trauma represent a multifactorial problem and are associated with patient age, comorbidities and preexisting conditions, fluid balance, use and dosing of nephrotoxic drugs such as vasopressors and antibiotics, sepsis, and number of operations, among others.[30–32] In agreement with Lin et al., we observed no disturbances of acid/base balance following the administration of high- or low-dose AA.[21]

A secondary endpoint of this analysis was efficacy of the administered treatments with AA in comparison to one another. A key finding in the original study by Tanaka et al was a dramatic 45% decrease in fluid requirements during acute resuscitation without significant alteration of hemodynamics.[19] Overall resuscitation volumes during the first 24 hours were trending lower in the HD group than with LDAA, without reaching statistical significance. Upon in-depth analysis of the administered fluids, a significant reduction was noted regarding the need for colloid fluid with HDAA. Vasopressor use also trended lower in the HD than in the LDAA group during the first 24 hours without reaching statistical significance. One reason for these observations may be that this trial did not include a control group of patients without any administration of AA and that even LDAA might have had some effect on fluid requirements, approximating the results of each group relative to one another. When considering the structure of our endpoint—data regarding the administration duration of AA, one notices a trending effect on several resuscitation parameters during the first 24 hours while HDAA was continuously administered (most notably total crystalloids infused and fluid balance); a compensatory partial reversal of these effects seems to occur at 72 hours postburn and discontinuation of AA administration. This study is underpowered to fully substantiate a conclusion; however, one possible hypothesis is, that the full effect of AA may not be observable due to too short administration duration. This hypothesis would be underscored by our measurements of significantly reduced serum AA concentrations in the HD group at 72 versus 24 hours and may justify the expansion of therapeutic administration to 72 or 96 hours as described in the safety study in septic patients by Fowler et al Again, large placebo-controlled dose- and duration-finding trials, addressing, and monitoring all potentially remaining safety concerns, are needed to conclusively answer this question.

Limitations

This study was retrospective by design and from a single center, which may have introduced selection or confounding bias. We acknowledge that our study was unable to demonstrate positive effects of HDAA on relevant clinical outcomes and underpowered to reliably detect adverse events. As with any single intervention in modern optimized burn care, especially one that takes place as early and shortly as HDAA administration for 24 hours immediately after admission, it can be difficult to directly associate heterogeneous clinical outcomes. Nonetheless, this has to be the standard against which any novel intervention needs to be held, as only improvement of clinical outcomes justifies modification of care. The lack of a placebo group, the short duration of administration, the different AA producers (LDAA: Rotexmedica GmbH Arzneimittelwerk, Trittau, Germany; HDAA: Pascoe, Giessen, Germany) as well as the relatively low number of patients might preclude us from drawing clinically meaningful conclusions at this point. We acknowledge the relatively low percentage of full thickness burn injury in our patient collective and hypothesize that potential effects of AA might be more pronounced in more severely burned patients. Regarding our volume resuscitation protocol we counted every instance of norepinephrine administration (including

short boluses during acute blood pressure drops in the shock phase) as a binary outcome, as more detailed data on doses and durations was not available for analysis. Lastly, we concede, that potentially lacking control for residual confounding may pose a limitation of this study.

Future prospective, randomized, controlled, and well-powered trials, which are not primarily focused on treatment safety but on its efficacy ought to be put in motion to conclusively confirm or disprove the positive effects so enthusiastically described by Tanaka et al 20 years ago.

CONCLUSION

HDAA administration increased AA plasma levels in burn patients and was not significantly associated with AKI, renal failure, disturbances in acid–base homeostasis, or any other investigated measure of adverse events. In this analysis, a reduction in colloid fluid requirements as well as trends towards reduced crystalloid fluid and vasopressor requirements during the first 24 hours postburn were noted. Large prospective studies are needed to investigate a therapeutic AA plasma concentration for burn patients and an optimal dosing and duration of AA administration.

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