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The effects of ω-3 fish oil emulsion-based parenteral nutrition plus combination treatment for acute paraquat poisoning

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Abstract

Objective: To investigate the effects of parenteral nutrition (PN) including ω-3 fish-oil emulsion on nutritional state, inflammatory response, and prognosis in patients with acute paraquat poisoning.

Methods: Patients randomized to receive medium chain triglycerides (MCT)/long chain triglycerides (LCT)-based PN (control group) or MCT/LCT-based PN containing ω-3 fish-oil emulsion (intervention group) were compared for 90-day survival and short-term treatment efficacy.

Results: Tumour necrosis factor-α levels were significantly lower in the intervention group ($n = 101$) versus controls ($n = 73$) on treatment days 4 and 7. Intervention group C-reactive protein (CRP) levels were significantly increased on day 4, decreased to baseline (day 1) levels on day 7, and were significantly lower than baseline on day 10. Control group CRP levels were significantly increased on days 4 and 7 versus baseline, and returned to baseline levels on day 10. On day 7, retinol binding protein had recovered to baseline levels in the intervention group only. Intervention group mortality rate (36.6%) was significantly lower than controls (57.5%). ω-3 fish-oil PN was associated with reduced risk of death (hazard ratio 0.52; 95% confidence interval 0.33, 0.82).

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Conclusion: In patients with acute paraquat poisoning, MCT/LCT with ω-3 fish-oil emulsion PN plus combination treatment advantageously attenuated the inflammatory response, modified the nutritional state, and was associated with significantly improved 90-day survival versus treatment without ω-3 fish oil.

Keywords
Paraquat poisoning, ω-3 fish oil fat emulsion, combination treatment, inflammatory factors

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Introduction

Paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride) is an effective and safe nonselective herbicide when used appropriately, however, it is highly toxic to humans.[1] Paraquat poisoning, which is mainly caused by intentional ingestion for suicide, is characterized by multiple organ failure due to excessive production of reactive oxygen species (ROS) and the subsequent inflammatory response.[2,3] Additionally, paraquat has been shown to increase the expression levels of inflammatory response genes, such as interleukin (*IL*)-1, *IL-6*, *IL-8*, tumour necrosis factor (*TNF*)-α, *TNF-β*, interferon-1, transforming growth factor (*TGF*)-β, and nuclear factor (*NF*)-kβ.[4] Pro-inflammatory cytokines, such as TNF-α and others, can induce ROS formation.[5,6] There is no targeted antidote for paraquat poisoning, and standard treatment includes a combination of cyclophosphamide, steroids, antioxidants, and haemperfusion, which has been demonstrated to be effective in preventing respiratory failure and significantly improves survival rates in moderate to severe cases.[7–10] Cyclophosphamide and glucocorticoid treatments have been associated with increased ROS production, however, which subsequently leads to oxidative stress, lipid peroxidation, glutathione consumption, increased glutathione peroxidase and superoxide dismutase activities, and glucocorticoid resistance accompanied by immunosuppression.[11–15]

Clinically, most patients with paraquat poisoning who have gastrointestinal tract injury have been found to develop feeding difficulties, and total parenteral nutrition (PN) is needed to reduce nutritional risks.[1,11,16–19] The most common parameters measured to evaluate nutritional status include body weight, triceps skinfold thickness, mid-arm circumference, and mid-arm muscle circumference,[20] however, these parameters are insensitive to early changes in the nutritional status of patients. Conversely, prealbumin (PA) and retinol binding protein (RBP) measurements are sensitive to early changes in nutritional status.[21,22] Thus, PA and RBP were used in the present study to evaluate short-term changes in nutrition status following treatment for acute paraquat poisoning.

Clinical nutrition has evolved and is considered to be a joint pharmacological/nutritional therapy in treating pro-inflammatory states, such as sepsis and acute respiratory distress syndrome.[23,24] Studies have revealed that PN containing an ω-3 fish-oil emulsion exhibits anti-inflammatory properties and can reduce the development of lung oedema and improve pulmonary function through decreasing the 4-series leukotrienes and

increasing release of the anti-inflammatory cytokines TGF-β, IL-10 and IL-13.[24–31] Intravenous ω-3 fish-oil emulsion administration also inhibits the 5-lipoxygenase pathway and the leukotriene B4-mediated function in inflammatory cells, and increases the production of specialized pro-resolving mediators that counter regulate pro-inflammatory mediators.[32–35]

Based on the above findings, the aim of the present study was to test the hypothesis that addition of PN containing an ω-3 fish-oil emulsion to combination therapy would beneficially ameliorate the altered nutritional state, decrease the inflammatory response, and potentially decrease the mortality rate in patients with paraquat poisoning.

Patients and methods

Study population

This prospective, randomized, controlled single-centre clinical trial was conducted at the Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China between January 2014 and December 2016, and included patients who conformed fully to the following criteria: aged 14–75 years with a clear past medical history and a normal nutrition state; a clear history of paraquat ingestion; admission to the Second Hospital of Hebei Medical University within 48 h of paraquat ingestion; and positive paraquat test in plasma. Patients who met any of the following criteria were excluded: aged < 14 years, pregnant, transcutaneous or intravenous paraquat exposure and undetectable levels of paraquat in the blood, combined drug exposure, transfer to another hospital during treatment or treatment abandonment, a history of chronic obstructive pulmonary disease, psychosis, or diabetes with severely impaired liver or renal function, hospital exit, or missing study data.

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Medical Review Board and Ethics Committee of the Second Hospital of Hebei Medical University. Written informed consent was obtained from patients or their legal guardians. All patient information was available to the clinicians only, and all the research data were analysed anonymously.

Treatment protocols

Consecutive, eligible participants were randomly allocated to the control group or the intervention group following baseline assessments. Randomization was conducted using a computer-generated randomization scheme.

Immediately upon baseline assessment and diagnosis, all patients were administered 100 g activated carbon tablets plus Fuller's earth via a gastric tube to minimize further absorption.[36] All patients also received a femoral venous dual lumen catheter with a blood flow rate of 150–200 ml/min × 2 h for a 6-h interval with HA330 resin haemperfusion (Jafron Biomedical Co. Ltd., Zhuhai City, China). Haemperfusion was discontinued in patients whose plasma paraquat concentration was < 50 ng/ml.

In addition, all patients received daily pulse methylprednisolone therapy (1 g; Pfizer Manufacturing Belgium NV, Rijksweg, Belgium) via intravenous infusion for three days and 15 mg/kg cyclophosphamide (Jiangsu Sheng Di Medicine Co., Ltd, Lianyungang, Jiangsu, China) for three days. The calorie intake for all patients was maintained at 20 kcal/kg/day. Novamin 8.5% (Huarui Pharmaceutical Co., Ltd., Wuxi, Jiangsu, China) was administered to provide 35–50% of the total calories and 0.15–0.20 g/kg/day nitrogen. Glucose and exogenous insulin (6:1 ratio), vitamins, electrolytes, trace elements, and water were administered via

central venous infusion for 10–12 h immediately following diagnosis. Both groups of patients received combination therapy, however, the control group received 0.6 g/kg Lipofundin 20%, a medium chain triglycerides (MCT)/long chain triglycerides (LCT)-based emulsion (Braun Melsungen AG, Melsungen, Germany), while the intervention group received 0.4 g/kg Lipofundin 20% plus 0.2 g/kg ω-3 fish-oil emulsion (Fresenius Kabi Huarui Pharmaceutical Co., Ltd., Sub packaging enterprises, Wuxi, Jiangsu, China). Treatment was continued for 10 days depending on survival. The two patient groups were given the same nutritional meals provided by the Nutrition Department of the Second Hospital of Hebei Medical University.

Outcome measures

The primary endpoint was overall 90-day mortality. The secondary endpoints included changes in inflammatory status (measured by total lymphocyte count [TLC], TNF-α and C-reactive protein [CRP] levels) and nutritional status (measured by serum RBP and prealbumin levels) following the administration of PN plus combination treatment.

Data collection

Sociodemographic and clinical characteristics were collected by systematically reviewing the patients' medical records. The Acute Physiology And Chronic Health Evaluation (APACHE) II score was calculated to classify the severity of disease following patient admission. Venous blood samples for biochemistry analyses were collected at 2 h following lipid infusion on days 1, 4, 7 and 10. Biochemical tests were performed mainly on fresh blood samples (a very small number of samples were centrifuged and stored at –80 °C prior to testing) according to standard hospital protocols, as patients with paraquat poisoning have priority to blood tests at the Second Hospital of Hebei Medical University. RBP and serum TNF-α levels were measured using commercially available kits for use with the DPC IMMULITE 1000 system (all Siemens Healthcare Ltd., Erlangen, Germany) according to the manufacturer's operating instructions. Levels of CRP, TLC and prealbumin were quantified using a Cobas Integra 700 chemistry analyser and reagents (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. These data were collected by postgraduate students unfamiliar with the study to avoid bias.

Statistical analyses

Data for continuous variables are presented as mean ± SD, and categorical variables are presented as n (%) prevalence. Between-group differences were statistically analysed using Student's t-test, paired t-test, or χ^2-test, as appropriate. Survival curves were estimated according to the Kaplan-Meier method, and treatments were compared using log-rank tests. Multivariable Cox proportional hazard models were applied to the outcome while controlling for possible confounding baseline characteristics, and results are presented as hazard ratios (HR) and 95% confidence intervals (CI). Statistical analyses were performed using SPSS software, version 18.0 (IBM Corporation, New York, NY, USA), and a P value <0.05 was considered statistically significant.

Results

A total of 238 patients who fulfilled the criteria for acute oral poisoning between January 2014 and December 2016 were included for enrolment into the study (Figure 1). Of these, 15 patients were

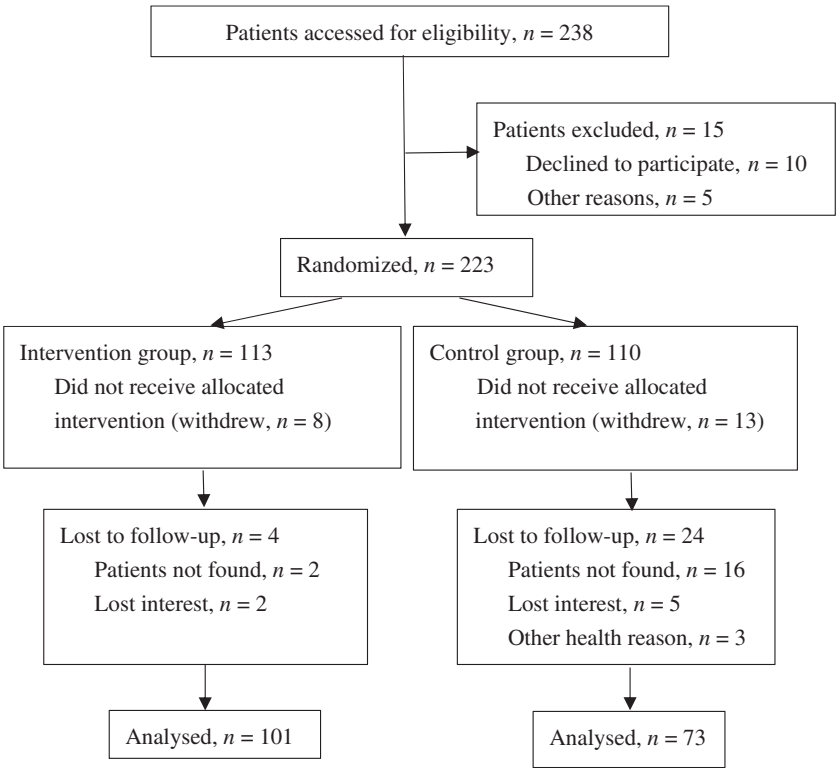

Figure 1. Study flow diagram showing selection and randomization to treatment with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention group) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control group) in patients with acute paraquat poisoning; MCT, medium chain triglycerides; LCT, long chain triglycerides

excluded either because they declined to participate ($n = 10$) or due to other reasons ($n = 5$). Thus, a total of 223 patients were enrolled and randomized to the two treatment groups: 113 patients in the intervention group and 110 patients in the control group. Twenty-one patients withdrew from the study and 28 patients were lost to follow-up, leaving 174 patients included in the final analyses (Figure 1). The final study population comprised 101 patients in the intervention group and 73 patients in the control group (mean age, 32.60 ± 12.03 years, range, 14–70 years; with 90 [51.7%] male patients and 84 [48.3%] female patients; Table 1). The mean time from paraquat ingestion to treatment was 3.20 ± 4.71 h (range, 25 min to 47 h). During hospitalization, there were no significant side effects associated with parenteral nutritional support, and there were no deaths.

There were no statistically significant between-group differences regarding demographics and baseline characteristics, time to treatment, nutritional (except RBP levels) and inflammatory indicators or APACHE II scores (all $P > 0.05$ except RBP, $P = 0.02$; Tables 1 and 2).

In terms of TLC, there were no statistically significant between-group differences on days 1 (baseline), 4, 7 or 10 (all $P > 0.05$; Table 2, Figure 2a). Within-group analyses showed that TLC was consistently reduced on days 4, 7, and 10 after

Table 1. Demographic and baseline characteristics in patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control)

Variable	Study group[a]	
	Intervention ($n = 101$)	Control ($n = 73$)
Sex, male: female	54:47	36:37
Age, years	32.46 ± 12.76	32.79 ± 11.01
Body mass index, kg/m^2	22.3 ± 16.8	22.4 ± 15.7
Baseline serum paraquat level, mg/l	6.92 ± 3.99	6.14 ± 3.97
Time to treatment, h	2.99 ± 3.71	3.49 ± 5.82
Baseline total protein, g/l	72.61 ± 7.31	72.56 ± 5.62
Baseline ALB, g/l	46.50 ± 5.27	46.09 ± 5.15
Baseline TC, mmol/l	4.42 ± 1.03	4.11 ± 0.99
Baseline haemoglobin, g/l	139.80 ± 22.13	136.78 ± 19.81
Baseline serum K^+ levels, mmol/l	3.86 ± 0.39	3.82 ± 0.43
Pleural effusion (yes/no)	34/67 (33.66%)	29/44 (39.73%)
Height, cm	167.5 (147–181)	169.2 (150–186)
APACHE II score	21.40 ± 3.48	21.7 ± 6.32

Data presented as *n* (%) prevalence, mean $\pm$ SD or median (range).
MCT, medium chain triglycerides; LCT, long chain triglycerides; ALB, albumin; TC, total cholesterol; APACHE, Acute Physiology And Chronic Health Evaluation.
[a]No statistically significant between-group differences ($P > 0.05$; Student's *t*-test, paired *t*-test, or χ^2-test).

initiation of treatment compared with baseline in both treatment groups (intervention group, baseline versus day 4, $P = 0.02$; baseline versus day 7, $P < 0.001$; baseline versus day 10, $P < 0.001$; control group, baseline versus day 4, 7 and 10, all $P < 0.001$; Figure 2b).

There was no statistically significant between-group difference in TNF-α levels at baseline (day 1 of admission; intervention versus control group, $P = 0.12$), however, there were statistically significant between-group differences on days 4 and 7 ($P < 0.001$; Table 2 and Figure 3a). This difference was due to a statistically significant decreasing trend in the intervention group on days 4 and 7 versus baseline (both $P < 0.001$; Figure 3b).

There were statistically significant between-group differences in CRP levels on days 7 and 10 ($P < 0.05$; Table 2 and Figure 4a). In both the intervention and control groups, CRP levels increased from the baseline reading to day 4 (both $P < 0.001$). In the intervention group, CRP levels then decreased to baseline levels on day 7 (baseline versus day 7, $P = 0.505$), and decreased to below baseline levels on day 10 (baseline versus day 10, $P < 0.001$). In the control group, CRP levels remained fairly stable at day 7 (day 7 versus baseline $P = 0.008$), but decreased back to baseline levels on day 10 (day 10 versus baseline, $P = 0.512$; Table 2 and Figure 4b).

In the intervention group, serum RBP levels were significantly higher than the control group on day 1 (baseline) and day 7 ($P = 0.02$ and $P < 0.001$, respectively; Figure 5a). In both groups, serum RBP levels were decreased on day 4 (intervention group baseline versus day 4, $P < 0.001$; control group baseline versus day 4, $P = 0.01$). On day 7, serum RBP levels in the

Table 2. Comparison of variables in patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control)

	Study group		
Analysis variable	Intervention, $n = 101$	Control, $n = 73$	Statistical significance
TLC, $\times 10^9$/l			
Baseline (day 1)	1.26 ± 0.63	1.24 ± 0.70	NS
Day 4	0.62 ± 0.76	0.46 ± 0.25	NS
Day 7	0.36 ± 0.40	0.34 ± 0.53	NS
Day10	0.24 ± 0.51	0.38 ± 0.36	NS
TNF-α, pg/ml			
Baseline (day 1)	31.89 ± 6.21	33.47 ± 6.92	NS
Day4	30.32 ± 5.51	34.43 ± 5.61	$P < 0.001$
Day7	27.81 ± 6.98	32.37 ± 6.82	$P < 0.001$
CRP, mg/l			
Baseline (day 1)	2.03 ± 2.13	2.08 ± 2.98	NS
Day4	3.22 ± 2.77	3.56 ± 2.78	NS
Day7	1.98 ± 2.13	3.38 ± 3.62	$P < 0.001$
Day10	1.01 ± 1.65	1.85 ± 3.02	$P = 0.02$
RBP, mg/l			
Baseline (day 1)	32.26 ± 6.73	29.72 ± 6.77	$P = 0.02$
Day 4	28.50 ± 6.68	27.24 ± 7.18	NS
Day 7	33.75 ± 7.80	27.05 ± 7.45	$P < 0.001$
PA, g/l			
Baseline (day 1)	0.25 ± 0.07	0.23 ± 0.07	NS
Day4	0.27 ± 0.16	0.24 ± 0.06	NS
Day7	0.30 ± 0.25	0.28 ± 0.26	NS
Day10	0.31 ± 0.31	0.29 ± 0.27	NS

Data presented as mean $\pm$ SD.
MCT, medium chain triglycerides; LCT, long chain triglycerides; TLC, total lymphocyte count; TNF, tumour necrosis factor; CRP, C-reactive protein; RBP, retinol binding protein; PA, prelabumin.
NS, no statistically significant between-group difference ($P > 0.05$; Student's *t*-test)

intervention group were higher than those on day 4 ($P < 0.001$ day 7 versus day 4), and had recovered to baseline levels ($P = 0.126$, baseline versus day 7). Control group RBP levels failed to return to baseline levels on day 7 ($P = 0.001$; Table 2 and Figure 5b).

Prealbumin levels were not significantly different between the two treatment groups at any time-point, and did not markedly change in either group following initiation of treatment (Table 2 and Figure 6a and b).

Sub-analyses of indices in the survivor and non-survivor groups (Table 3) revealed statistically significant between-group differences in baseline prealbumin levels (0.25 versus 0.23 g/l), the proportion of patients with pleural effusion (25.3% versus 49.4%), changes in RBP, CRP and TNF-α levels, and the proportion of patients who had received ω-3 fish-oil emulsion (67.4% versus 46.8%, survivor versus non-survivor, respectively).

During the 90-day follow-up period, 95 patients had survived following oral ingestion of paraquat and 79 patients had died. The 90-day mortality rates were as

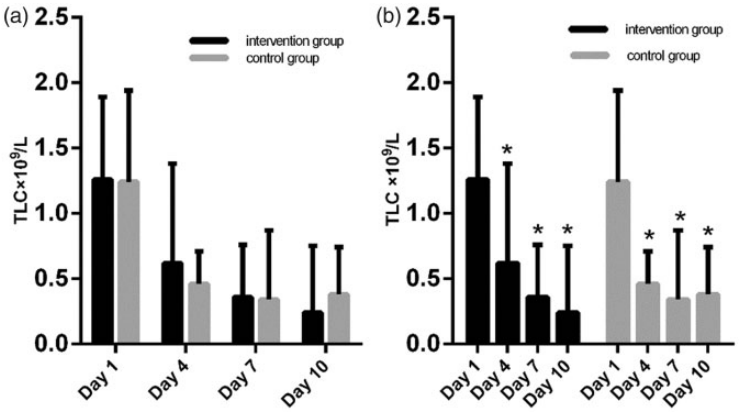

Figure 2. Comparison of total lymphocyte count (TLC) between patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention group) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control group), and within-group comparisons on each day following initiation of treatment: $^{*}P < 0.05$ versus baseline values (intragroup comparison using Student's *t*-test); No statistically significant differences between the two groups on each treatment day; MCT, medium chain triglycerides; LCT, long chain triglycerides

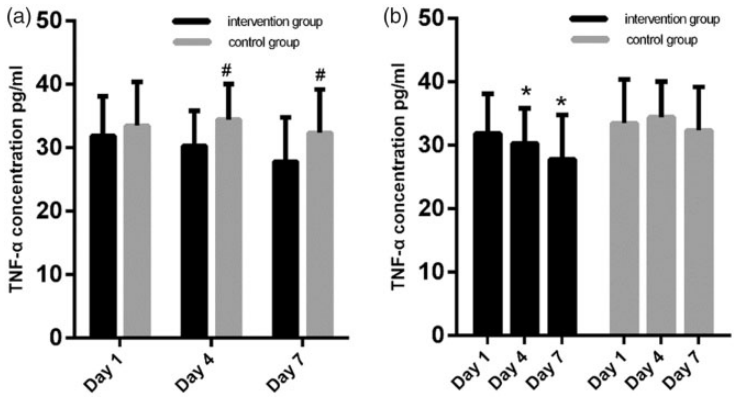

Figure 3. Comparison of tumour necrosis factor (TNF)-α levels between patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention group) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control group), and within-group comparisons on each day following initiation of treatment: $^{\#}P < 0.05$, between-group differences at days 4 and 7; $^{*}P < 0.05$, versus baseline (all Student's *t*-test); MCT, medium chain triglycerides; LCT, long chain triglycerides

follows: 37/101 patients in the intervention group (36.6%) and 42/73 patients in the control group (57.5%; $P = 0.006$). In multivariable Cox proportional hazard regression models, ω-3 fish-oil PN was associated with a reduced risk of death after adjusting for baseline variables (HR 0.52; 95% CI 0.33, 0.82; $P = 0.005$; Table 4 and Figure 7). Existing pleural effusion, RBP (day 7–day 1) decreases and

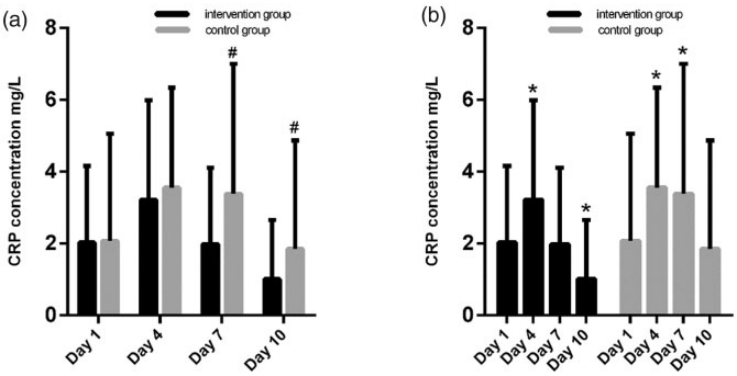

Figure 4. Comparison of C-reactive protein (CRP) levels between patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention group) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control group), and within-group comparisons on each day following initiation of treatment: $^{\#}P < 0.05$, between-group differences at days 7 and 10; $^{*}P < 0.05$, versus baseline (all Student's *t*-test); MCT, medium chain triglycerides; LCT, long chain triglycerides

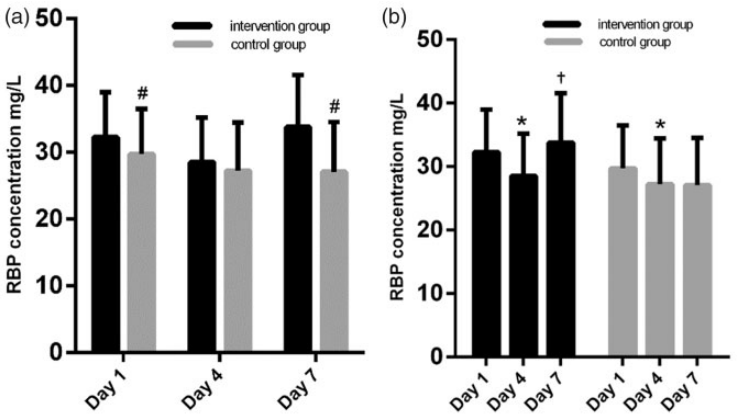

Figure 5. Comparison of retinol binding protein (RBP) levels between patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention group) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control group), and within-group comparisons on each day following initiation of treatment: $^{\#}P < 0.05$, between-group differences at days 1 and 7; $^{*}P < 0.05$, versus baseline; $^{\dagger}P < 0.05$, day 4 versus day 7 (all Student's *t*-test); MCT, medium chain triglycerides; LCT, long chain triglycerides

TNF-α (day 7–day 1) increases were associated with an increased risk of death (HR 2.985, 95% CI 1.849, 4.704 [P <0.001]; HR 2.015, 95% CI 1.271, 3.196 [$P = 0.003$]; and HR 2.308, 95% CI, 1.438, 3.706 [$P = 0.001$], respectively; Table 4).

Discussion

The high mortality rates associated with paraquat poisoning are due largely to a lack of effective treatments.[10,37,38] Paraquat ingestion induces ROS generation, leading to lipid peroxidation-induced

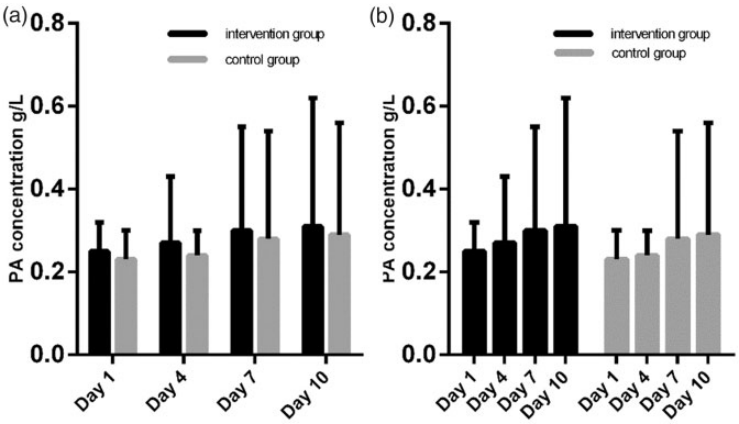

Figure 6. Comparison of prealbumin (PA) levels between patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention group) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control group), and within-group comparisons on each day following initiation of treatment: There were no statistically significant between-group or within-group differences (Student's *t*-test)

Table 3. Comparison of indices in survivor versus non-survivor patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control)

	Study group		
Variable	Non-survivors ($n = 79$)	Survivors ($n = 95$)	Statistical significance
Sex, male: female	42:37	48:47	NS
Age, years	34.33 ± 12.45	31.16 ± 11.53	NS
Body mass index, kg/m^2	22.4 ± 15.8	22.5 ± 12.7	NS
Baseline serum paraquat level, mg/l	6.81 ± 3.96	6.42 ± 4.02	NS
Time to treatment, h	3.71 ± 6.31	2.77 ± 2.71	NS
Baseline haemoglobin, g/l	138.99 ± 21.31	138.16 ± 21.17	NS
Total protein, g/l	72.80 ± 6.09	72.42 ± 7.08	NS
Baseline PA, g/l	0.23 ± 0.07	0.25 ± 0.07	$P = 0.02$
ALB	46.71 ± 4.23	46.01 ± 5.91	NS
TC, mmol/l	4.32 ± 1.07	4.27 ± 0.98	NS
Baseline serum K^+ level, mmol/l	3.85 ± 0.38	3.84 ± 0.43	NS
Pleural effusion, yes/no	39/40 (49.37%)	24/71 (25.26%)	$P < 0.001$
Change in RBP, day 7–day 1	48^+ /31^- (60.76%)	76^+/19^- (80%)	$P = 0.01$
Change in CRP, day 7– day 1	26^+/53^- (32.91%)	12^+/83^- (12.63%)	$P < 0.001$
ω-3 fish oil PN (yes/no)	37/42 (46.84%)	64/31 (67.37%)	$P = 0.01$
Change in TNF-α, day 7–day 1	26^+/53^- (32.91%)	12^+/83^- (12.63%)	$P < 0.001$

MCT, medium chain triglycerides; LCT, long chain triglycerides; PA, prealbumin; ALB, albumin; TC, total cholesterol; RBP, retinol binding protein; CRP, C-reactive protein; PN, parenteral nutrition; TNF, tumour necrosis factor.
+ increase or no decrease; –decrease.
NS, no statistically significant between-group difference ($P > 0.05$; Student's *t*-test or χ^2-test).

Table 4. Regression analyses using cox proportional hazards models summarising the clinical indices predicting mortality in patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control)

	Univariate Cox Model		Multivariate Cox Model	
Index	HR (95% CI)	Statistical significance	Adjusted HR (95% CI)	Statistical significance
Pleural effusion	2.907 (1.862, 4.539)	$P < 0.001$	2.985 (1.849, 4.704)	$P < 0.001$
Change in RBP↓ (day 7–day 1)	1.874 (1.191, 2.950)	$P = 0.007$	2.015 (1.271, 3.196)	$P = 0.003$
Change in TNF↑ (day 7–day 1)	2.306 (1.438, 3.698)	$P = 0.001$	2.308 (1.438, 3.706)	$P = 0.001$
ω-3 fish oil PN	0.509 (0.327, 0.793)	$P = 0.003$	0.522 (0.332, 0.820)	$P = 0.005$
Change in PA↓ (day 7–day 1)	1.683 (1.077, 2.629)	$P = 0.022$	1.323 (0.836, 2.094)	NS

MCT, medium chain triglycerides; LCT, long chain triglycerides; HR, hazard ratio; CI, confidence interval; RBP, retinol binding protein; TNF, tumour necrosis factor; PN, parenteral nutrition, PA, prealbumin.
NS, no statistically significant correlation ($P > 0.05$).

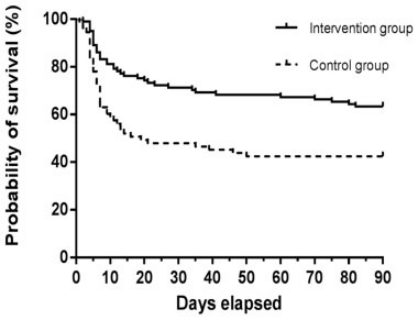

Figure 7. Kaplan-Meier estimates of the probability of survival at 90 days between patients with acute paraquat poisoning treated with 0.4 g/kg lipofundin 20% MCT/LCT-based emulsion plus 0.2 g/kg ω-3 fish-oil emulsion (intervention group) or 0.6 g/kg lipofundin 20% MCT/LCT-based emulsion (control group): Hazard ratio 0.522, 95% confidence interval 0.332, 0.820 ($P = 0.005$)

cellular damage and the activation of many types of inflammatory cytokines. The activation of this cascade may lead to subsequent damage to the mitochondria and cell apoptosis at the organ level. These effects may result in conditions such as pneumonitis and fibrosis of the lungs, and renal and liver damage.[11,28,39–41] TNF-α is considered a promising inflammatory marker in the early stages of acute lung injury induced by paraquat poisoning. CRP, with a half-life of 4–6 h, is a key acute-phase protein, and CRP levels generally return to normal within 3–7 days of the cessation of inflammation.[42] In the present study, following the initiation of ω-3 fish-oil emulsion treatment, TNF-α levels in the intervention group gradually decreased and were significantly lower than those in the control group at days 4 and 7. In contrast, TNF-α levels showed no significant decrease in the control group. Intervention-group CRP levels were increased at day 4, then returned to baseline levels on day 7 and fell below baseline levels on day 10. In the control group, however, CRP levels remained increased on day 7, and had not decreased below baseline levels by day 10. The initial increased levels of TNF-α and CRP were normalized by the infusion of ω-3 fish-oil emulsion-based PN treatment in the intervention group, suggesting protective effects of ω-3 fish-oil emulsion-based PN against paraquat-induced inflammation in cases of acute paraquat poisoning. Lipid emulsions containing ω-3 fatty acids have been shown to attenuate inflammatory activity via inhibiting the toll-like receptor (TLR)4

and nucleotide-binding oligomerization domain (NOD) signalling pathways, which subsequently activate NF-κβ signalling, downregulate the secretion of pro-inflammatory cytokines, such as TNF-a, IL-6, and CRP, and positively affect patient prognosis.[43,44] Other research has demonstrated that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can scavenge intracellular ROS and attenuate oxidative stress through upregulating the nuclear factor erythroid 2-related factor 2 (NRF2)-mediated antioxidant response.[45,46]

The recent discovery of specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, protectins and maresins, has indicated the anti-inflammatory mechanism of ω-3 fatty acids.[32] SPMs in the host govern the extent and duration of the inflammatory response, which is related to the patient's prognosis.[47] Intravenous administration of ω-3 fatty acids affects SPM levels in plasma, and this may be associated with better outcomes in acutely ill patients.[33]

Plasma PA and RBP have short half-lives (1/2 day) and are often used to measure changes in the nutritional state over short periods of time.[21,22] The negative association between serum PA levels and clinical outcomes has been demonstrated in many types of diseases.[48] In the current study, according to nutritional status based on RBP and PA levels, PA was not markedly increased in the two groups following initiation of treatment, which may be partly explained by the relatively small dosage of ω-3 fatty acids or the short period of administration. However, hepatic protein synthesis is also influenced by acute inflammation, which decreases PA production.[49]

In the present study, RBP levels in the intervention group had recovered to baseline levels on day 7, but remained low in the control group. A previous study revealed that patients receiving a combination emulsion had better liver tolerance than those receiving a soybean oil-based lipid emulsion alone.[50] This finding may be due to the role of ω-3 fatty acids in increasing liver blood perfusion and reversing steatosis and cholestasis,[51,52] and these effects may have contributed to reducing the hepatic damage from acute paraquat poisoning. These findings support the hypothesis that ω-3 fish-oil emulsion-based PN advantageously modifies the nutritional state compared with an MCT/LCT-based fat emulsion.

A total of 174 patients were included in the present study, with 95 survivors and 79 deaths equating to a total mortality rate of 45.4% during the 90-day follow-up. The mortality rate was lower in the intervention group than in the control group, and this decreased mortality may be due to the anti-inflammatory and protective hepatic effects of ω-3 fish-oil PN.

Paraquat concentration-time data are often used as tools to predict patient prognosis in cases of paraquat poisoning, however, this tool appears only to be useful within a relatively limited time window.[53] For instance, when the time from ingestion to treatment is <4 h, this tool incorrectly predicts death or survival.[54] In the present study, 66.67% of patients had a time to treatment of < 4 h, which may explain why baseline serum paraquat levels and time to treatment were not found to be correlated with paraquat prognosis.

Through Cox proportional hazards models analyses, ω-3 fish oil PN was found to be associated with a reduced risk of death following paraquat ingestion. Existing pleural effusion, RBP (day 7– day 1) decreases and TNF-α (day 7–day 1) increases were associated with an increased risk of death.

The present results may be limited by a number of factors. The cases included in the present study were obtained from a relatively small, single-centre sample, and thus, may not be truly representative of the

wider population. In addition, there were potential sampling biases, as only 73% of those who met inclusion criteria were included in the final analysis. No placebo group was used due to ethical concerns of non-treatment.

In conclusion, the current study showed that, compared with MCT/LCT-based fat emulsion treatment, ω-3 fish-oil emulsion-based PN plus combination treatment is advantageous in attenuating the inflammatory response, modifying the nutritional state, and in significantly improving 90-day survival rates in patients with acute paraquat poisoning. Future well-designed prospective, multicentre, randomized-controlled trials are essential to build on the results of the current study in establishing the use of PN containing ω-3-rich fish oil as an effective paraquat poisoning therapy.

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Declaration of conflicting interests

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