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## Antioxidant supplementation for the treatment of acute lung injury: a meta-analysis

*Suplementação de antioxidantes no tratamento da lesão pulmonar aguda: meta-análise*

### ABSTRACT

**Objective:** This meta-analysis was performed to evaluate the evidence supporting antioxidant supplementation as an adjunct therapy to prevent oxidative damage and improve the clinical outcomes (mortality, length of hospital stay and duration of mechanical ventilation).

**Methods:** The search strategy for randomized controlled trials (RCTs) involved the participation of two researchers who independently assessed the methodological quality of each full-text article that was available in the PubMed, ISI WEB of Knowledge and ScienceDirect databases.

**Results:** We extracted 110 studies from the past 10 years, but only

30 articles met the methodological criteria (RCT, blinded and statistically significant results), for a total of 241 animals and 256 patients. This study found an odds ratio (OR) of 0.45 [95% confidence interval (CI): 0.26 to 0.79] for death in the experimental group compared with placebo (six trials, n = 256), an OR of 0.46 [95% CI: 0.26 to 0.87] for hospitalization time and an OR of 0.63 [95% CI: 0.35 to 1.12] for mechanical ventilation time between groups.

**Conclusion:** Conflicting evidence makes it impossible to recommend the routine use of antioxidant supplementation in critically ill patients.

**Keywords:** Antioxidants/therapeutic use; Acute lung injury/drug therapy; Free radicals

### INTRODUCTION

Antioxidant supplementation<sup>(1-3)</sup> may prolong the initial phase or inhibit the propagation phase of reactive oxygen species (ROS) and reactive nitrogen species (RNS).<sup>(4)</sup> Disrupted oxidant-antioxidant balance has a major role in the genesis of inflammatory diseases, such as acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).<sup>(5,6)</sup> Antioxidants have been traditionally administered via oral,<sup>(3)</sup> intraperitoneal<sup>(1)</sup> or intravenous<sup>(2)</sup> routes. Patients with ARDS have a significant decrease when compared to healthy subjects at concentrations of reduced glutathione (138 ± 25 vs. 7 ± 4 μM), ascorbic acid (85 ± 21 vs. 27 ± 10 μM) concentrations in the bronchoalveolar lavage fluid (BALF), α-tocopherol (11.46 ± 0.55 vs. 7.73 ± 0.54 mg/L), β-carotene and selenium.<sup>(7,8)</sup> The plasma concentrations of lipid peroxides are also significantly increased versus controls [e.g., malondialdehyde (MDA), 2.2 vs. 1.3 nM].<sup>(9,10)</sup>

Additionally, patients with ARDS or patients who are at risk of ARDS show significantly reduced plasma polyunsaturated fatty acid concentrations

(linolenic acid,  $26.9 \pm 4.6$  vs.  $18.5 \pm 4.8$  nM; arachidonic acid,  $11.7 \pm 1.68$  vs.  $8.33 \pm 2.46$  nM; eicosapentaenoic acid,  $0.25 \pm 0.14$  vs.  $0.017 \pm 0.004$  nM), suggesting that ARDS is directly related to essential fatty acid deficiency.<sup>(10)</sup> ARDS patients also have significantly reduced plasma nitric oxide (NO) ( $1.7$  vs.  $0.7$   $\mu$ M).<sup>(9,11)</sup> However, NO actions may be either beneficial or harmful,<sup>(12)</sup> as it may either show protective effects or be a peroxynitrite pro-oxidant precursor.

### Participation of neutrophils and macrophages

The accumulation of plasma neutrophils and macrophages (polymorphonuclear leukocytes  $5 \times 10^6$  vs.  $4 \times 10^6$  cells/mL; BALF macrophages  $12 \times 10^6$  vs.  $1 \times 10^6$  cells/mL) plays a significant role in acute lung injury [compared with controls: myeloperoxidase (MPO) activity,  $15$  vs.  $5$  nmol/min/lung,  $p < 0.05$ ; neutrophil elastase activity,  $10$  vs.  $2.5 \times 10$  nmol/mL,  $p < 0.05$ ; BALF total protein,  $7$  vs.  $3$  mg/mL,  $p < 0.05$ ];<sup>(13,14)</sup> however, as ARDS may occur in neutropenic patients, the influence of other inflammatory markers is possible, including the involvement of other cell types and non-biochemical factors.<sup>(15)</sup> The defensive physiologic role of neutrophils is mediated by the release of not only ROS but also proteases (e.g., elastase). Effective neutralization of free radicals and proteases by antioxidants (plasma vitamin C,  $80$   $\mu$ mol/L) and antiproteases (plasma  $\alpha$ 1-antitrypsin  $54$   $\mu$ mol/L and  $\alpha$ 2-macroglobulin  $3$   $\mu$ mol/L),<sup>(13)</sup> prevents exacerbation of lung injury.<sup>(16)</sup> There are indications<sup>(17)</sup> that the formation of pulmonary edema, which is commonly found in ARDS patients, results from increased neutrophil-induced release of hydrogen peroxide ( $H_2O_2$ ), hydroxyl radical ( $\cdot OH$ ), and superoxide anion ( $O_2^-$ ) (5 minutes after lung injury:  $[O_2^-]$   $4$  vs.  $9$  nM/L/min).<sup>(13)</sup> The protease-antiprotease and oxidant-antioxidant imbalances may play important roles in ARDS pathogenesis.<sup>(18)</sup>

### METHODS

The initial search strategy involved two investigators independently assessing each paper's methodological quality. These were full-text articles found in the Pubmed, ScienceDirect and ISI Web of knowledge databases. The use of supplementary antioxidants in patients with acute lung injury or acute respiratory distress syndrome was chosen as the investigation focus. Later, randomized clinical trials (RCTs) and blinded trials were searched. Additionally, the authors attempted to standardize the evaluation of the trials'

methodological quality using the PEDro scale as an internal validation criterion. The outcomes that were considered relevant in this search were as follows:

- Oxidative damage (lipid peroxidation, protein carbonylation, or DNA oxidation);
- Inflammatory and immune response;
- Tissue injury;
- Mortality;
- Length of hospital stay;
- Assisted mechanical ventilation time.

For the search strategy, to avoid overlooking studies that mentioned the outcomes of interest only in the full text but not in the abstract, we chose not to use words related to the outcomes of interest. The search strategies used were as follows. For Pubmed: Clinical Trial OR Randomized Controlled Trial OR Clinical Trial AND Phase I OR Clinical Trial AND Phase II OR Clinical Trial AND Phase III OR Clinical Trial AND Phase IV OR Controlled Clinical Trial AND published in the last 10 years. For ScienceDirect and ISI Web of knowledge: Journals AND all sources AND all sciences AND published in the last 10 years. The following MESH key word combinations were used: [supplementation AND acute lung injury OR acute respiratory distress syndrome OR oxidative damage OR outcome OR injury OR antioxidants].

All abstracts published prior to June 17, 2010 were assessed. Those describing the study design and comparing antioxidant versus placebo or other active drug were selected and the full text was searched. Abstracts that may have led to studies that were not published in the databanks, studies that were ongoing studies, or studies that were available only in academic theses were not searched. We also searched the papers' references for other possible relevant studies. The evidence was assessed using a meta-analysis. A pragmatic inclusion criterion was chosen, including all RCTs with pre-specified outcomes, followed by methodological analysis using the PEDro score system. When the PEDro score was less than 3, the study was excluded for methodological insufficiency. According to the current recommendations, these were considered the most relevant criteria:

- Description of the sample size calculation;
- Description of the concealment of the randomization list;
- Use of blinded methods.

The lack of an explicit description of a concealed randomization list – which could include terms, such as central randomization, web-based randomization,

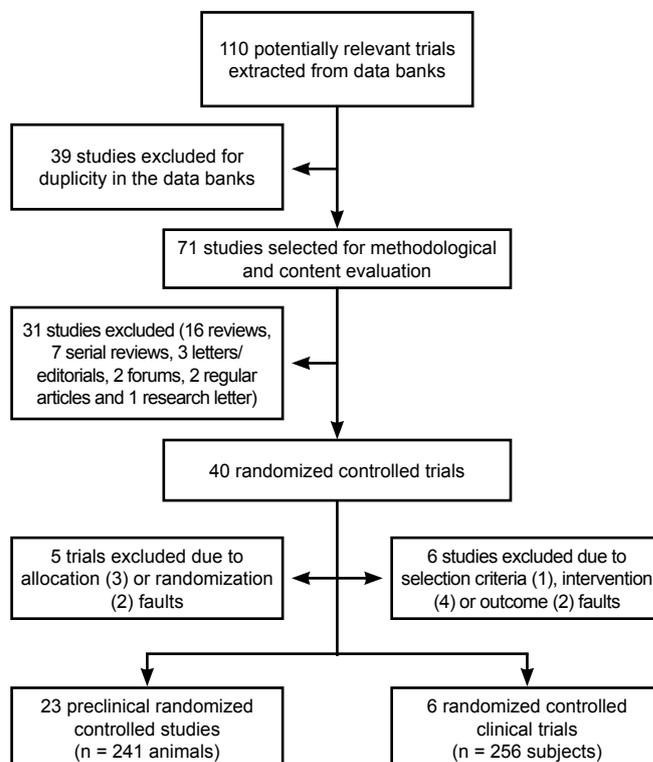
central phone randomization, or a clear statement on randomization list concealment – led to the conclusion of an unmet criterion. In terms of blinding, studies that were described as open-label and those lacking any blinding description were considered to not be blinded. To facilitate interpretation, the relative risk (RR) association was chosen for the assessment. The calculations were processed with the Mantel-Haenszel fixed effects method. Heterogeneity was assessed with the inconsistency test ( $I_2$ ), with values below 25% considered low heterogeneity. For these analyses, meta-analysis calculations were re-processed excluding the studies that failed to meet some quality criteria. Additionally, the main results calculations (i.e., with all studies included) were re-calculated using the fixed effects method, in addition to the calculation of odds ratios (ORs) with 95% confidence intervals (CIs) instead of RRs. The funnel plot was used to evaluate the publication bias impact. The analyses were conducted with R software, version 2.12.1.

## RESULTS

The search strategy identified 9 studies in Pubmed, 11 in ISI Web of Knowledge and 90 in ScienceDirect, for a total of 110 potentially relevant papers. The 81 studies discarded in this phase are detailed in Figure 1. In the comparison versus the placebo group, we found an OR of 0.45 [95% CI: 0.26–0.79] for death (six trials,  $n = 256$ ), an OR of 0.46 [95% CI: 0.26–0.87] for the length of hospital stay and an OR of 0.63 [95% CI: 0.35–1.12] for the mechanical ventilation time (Tables 1, 2 and 3). The outcomes targeted in our study, such as tissue injury and organ failure, could not be evaluated in this review. The 110 potentially relevant papers included 16 reviews, 7 serial reviews, 3 letters/editorials, 2 forums, 2 regular articles, 1 research letter, and 40 RCTs (33 pre-clinical and 17 clinical). Of the 40 available RCTs, only 29

reported the outcomes of interest. The more common outcomes of the excluded RCTs were changes in hemodynamic, histopathological and kinetic marker parameters.

The most common primary endpoint of the included studies was oxidative damage (lipid peroxidation, protein carbonylation and thiol group balance and anti-oxidative enzyme changes), which was individually reported in 24 of the 40 studies. As secondary endpoints,



**Figure 1 – Results of the search strategy of the PubMed, ScienceDirect and ISI WEB of Knowledge databases for antioxidant supplementation + oxidative damage studies (lipid peroxidation, protein carboxylation, oxo-8-gdG) + morbidity (mortality, length of hospital stay and assisted mechanical ventilation time) induced by acute lung injury or acute respiratory distress syndrome.**

**Table 1 – Meta-analysis of the effects of antioxidant supplementation versus placebo or no treatment on mortality rate**

Trial	Intervention group Deaths/Total	Control group Deaths/Total	OR	95% CI	%W (fixed)
Moradi et al., 2009 <sup>(19)</sup>	5/14	10/13	0.1667	[0.0307; 0.9042]	18.00
Pontes-Arruda et al., 2006 <sup>(20)</sup>	18/55	25/48	0.4476	[0.2014; 0.9948]	48.48
Nathens et al, 2002 <sup>(28)</sup>	4/94	7/81	0.4698	[0.1324; 1.6670]	19.44
Bernard et al., 1997 <sup>(27)</sup>	11/31	6/15	0.8250	[0.2321; 2.9325]	14.08
Total patients	194	157			
Total deaths	28	48			

Quantifying heterogeneity:  $\tau^2 < 0.0001$ ;  $H = 1$  [1; 2.19];  $I^2 = 0\%$  [0%; 79.2%]. Test of heterogeneity:  $Q=2.2$ ; d.f.=3.0;  $p$  value = 0.531. Method: Mantel-Haenszel.

**Table 2 – Meta-analysis of the effects of antioxidant supplementation versus placebo or no treatment on hospitalization and ICU time**

Trial	Intervention group ICU days/Total	Control group ICU days/Total	OR	95%CI	%W(fixed)
Moradi et al., 2009 <sup>(19)</sup>	32/39	42/50	0.9470	[0.3264; 2.7472]	22.16
Pontes-Arruda et al., 2006 <sup>(20)</sup>	17/28	13/28	0.3147	[0.0978; 1.0129]	32.58
Nathens et al, 2002 <sup>(28)</sup>	5/28	9/28	0.7667	[0.1828; 3.2158]	13.67
Bernard et al., 1997 <sup>(27)</sup>	20/30	30/30	0.1919	[0.0471; 0.7822]	31.58
Total days	125	136			
Total days in ICU	74	94			

ICU – intensive care unit. Quantifying heterogeneity: tau<sup>2</sup> = 0.1512; H = 1.17 [1; 1.91]; I<sup>2</sup> = 27% [0%; 72.6%]. Test of heterogeneity: Q= 4.11; d.f.= 3; p value= 0.2497. Method: Mantel-Haenszel.

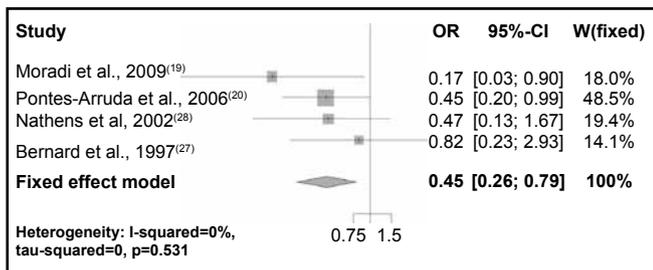
**Table 3 – Meta-analysis of the effects of antioxidant supplementation versus placebo or no treatment on assisted mechanical ventilation time**

Trial	Intervention group Days/Total	Control group Days/Total	OR	95%CI	%W(fixed)
Moradi et al., 2009 <sup>(19)</sup>	25/33	33/43	0.87	[0.29; 2.,65]	22.4
Pontes-Arruda et al., 2006 <sup>(20)</sup>	15/28	22/28	1.78	[0.62; 5.15]	17.3
Nathens et al, 2002 <sup>(28)</sup>	4/28	5/28	0.046	[0.13; 1.60]	25.1
Bernard et al., 1997 <sup>(27)</sup>	19/30	27/30	0.03	[0.00; 0.58]	35.1
Total days	119	129			
Mechanical ventilation days	63	87			

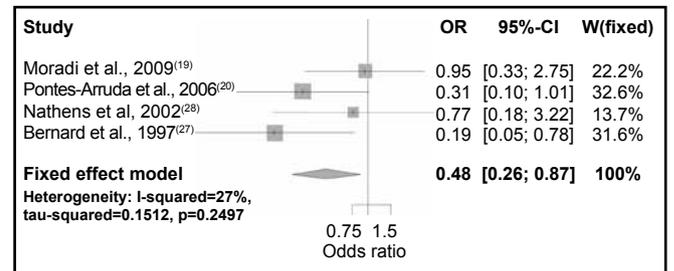
Quantifying heterogeneity: tau<sup>2</sup> = 0.8192; H = 1.67 [1; 2.87]; I<sup>2</sup> = 64% [0%; 87.8%]. Test of heterogeneity: Q = 8.33; d.f. = 3; p value=0.0397. Method: Mantel-Haenszel.

we analyzed the mortality rate associated with the length of hospital stay and assisted mechanical ventilation time. The time before supplementation ranged between 6 hours and 28 days (Chart 1). Moradi<sup>(19)</sup> reported reduced but not statistically significant mortality rate and hospital length of stay; however, the reduction of mechanical ventilation time was statistically significant. Of the six clinical trials that were available to assess the associations between supplementation and mortality rate, length of hospital stay and mechanical ventilation time, only four compared the treated patients with a placebo or untreated group (Figures 2, 3 and 4). One study analyzed the immune responses mediated by the cytokines, IL-1, IL-6, IL-8 and TNF $\alpha$ , which were associated with alveolar damage (with no statistically significant difference). Only the paper by Pontes-

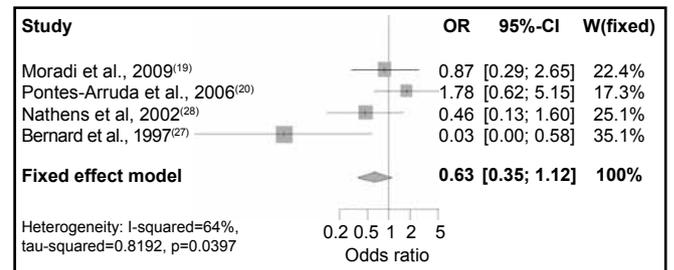
Arruda<sup>(20)</sup> found that the main adverse events associated with antioxidants were gastrointestinal effects, such as diarrhea and dyspepsia, but these associations not statistically significant.



**Figure 2 - Meta-analysis of the effects of antioxidant supplementation versus placebo or no treatment on mortality rate.**



**Figure 3 – Meta-analysis of the effects of antioxidant supplementation versus placebo or no treatment on hospitalization time.**



**Figure 4 – Meta-analysis of the effects of antioxidant supplementation versus placebo or no treatment on assisted mechanical ventilation time.**

**Chart 1 – Characteristics of clinical trials on the effects of antioxidant supplementation in acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) patients**

Trial	Supplementation	Intervention group		Control group	Via	Intervention	Follow-up time	Outcomes	Methodology quality*		
		N/Total	N/Total						Sample size calculation	Allocation	Blinding
Moradi et al., 2009 <sup>(19)</sup>	NAC	14/15	13/15	iv	150 mg (fist day) + 50 mg/kg/day	3 days	Increased oxygenation ratio, reduced mortality rate, unchanged mechanical ventilation time.	Unclear	Yes	Yes	
Pontes-Arruda et al., 2006 <sup>(20)</sup>	EPA, GLA, Taurine, vit C and E	37/55	23/48	Enteral	EPA (4.5 g/L), GLA (4.3 g/L) e (320 IU/L vitamin E, 840 mg/L vitamin C and 320 mg/L taurine)	28 days	Reduced mortality rate, mechanical ventilation time and length of ICU stay; unchanged oxygenation ratio.	Unclear	Yes	Yes	
Nathens et al., 2002 <sup>(28)</sup>	vit C and E	94/301	81/294	Enteral	100 mg ascorbic acid and 10 IU α-tocopherol daily	28 days	Reduced pneumonia and ARDS ratio, mechanical ventilation time, hospitalization time, mortality rate and BALF F <sub>2ac</sub> , IL-1, IL-6 and TNF-α levels.	Unclear	Yes	Yes	
Kumar et al., 2000 <sup>(9)</sup>	PUFA	20/20	12/12	NR	[EPA<0.017; DHA<1.85; GLA<0.025; AA<8.33 g/L]	6 hours	Low PUFA supplementation increased MDA and reduced nitric oxide levels.	Unclear	Yes	Yes	
Bernard et al., 1997 <sup>(27)</sup>	NAC and OTZ	12/31	11/15	iv	NAC (70 mg/kg) and OTZ (63 mg/kg), every 8 hours	10 days	Improved cardiac index, increased glutathione level, reduced hospitalization time, but failed to affect the mortality rate; no differences in BALF neutrophil counts.	Unclear	Yes	Yes	
Richard et al., 1990 <sup>(8)</sup>	vit E	12/12	17/17	NR	[plasma Vit E] < 7.73 mg/dL	NR	Low vitamin E supplementation increased lipid peroxidation	Unclear	Yes	Unclear	

NR – not reported; iv– intravenous; EPA – eicosapentaenoic acid; GLA – gamma-linolenic acid; AA – arachidonic acid; DHA – dihomogammalinolenic acid; NAC – n-acetylcysteine; OTZ – procysteine; vit C – ascorbic acid; vit E – α-tocopherol; PUFA – polyunsaturated fatty acids; IL – interleukin; TNF- α – tumor necrosis factor alpha; F<sub>2ac</sub> – isoprostane; BALF – bronchoalveolar lavage fluid. \*CONSORT group, PEDro scale.

## DISCUSSION

### Pre-clinical studies

A strategy to limit oxidative lung injury is to increase intracellular glutathione (GSH) content by use of its precursors, such as N-acetylcysteine (NAC).<sup>(13)</sup> GSH has vital protective functions against oxidative stress in the lungs, both intra- and extra-cellularly.<sup>(15)</sup> The synthesis of GSH depends on glutamylcysteine ligase (GCL). The inhibition of GCL inhibits GSH and consequently induces apoptosis. The promoter region (5'-flanking) of the GCL gene is regulated by activating protein-1 and is modulated by oxidant agents, phenolic antioxidants and several growth factors. GSH metabolism alterations, both in alveoli and lung tissue, are the central feature in many lung diseases.<sup>(21,22)</sup>

NAC may stimulate GSH synthesis, increase glutathione-S-transferase (GST) activity and have direct action on free radicals. NAC administration does not significantly reduce lung tissue MPO activity or MDA or 3-nitrotyrosine (3-NT) level.<sup>(23)</sup> NAC absorption and intracellular concentration may be increased by the use of liposomes (L-NAC). L-NAC (25 mg/kg intravenous) pre-treatment results in significantly increased non-thiol proteins and NAC levels in lung homogenates ( $p < 0.05$ ) and BALF ( $p < 0.001$ ). The liposomal formulation (L-NAC) is more effective than conventional NAC formulations for attenuating *E. coli* (lipopolysaccharide, LPS) endotoxin-induced lung injuries. NAC supplementation in LPS-exposed animals reduces lung edema, lipid peroxidation, damage to angiotensin-converting enzyme (ACE), chloramine concentration, and the concentrations of the eicosanoids thromboxane and leukotrienes (LTB2 and LTB4) in the lung.<sup>(24,25)</sup>

Hyperoxia and lung infections increase the risk of acute and chronic lung injury, but it is not clear if hyperoxia directly increases the risk of pneumonia. Arita et al.<sup>(26)</sup> evaluated the effects of antioxidants on the antimicrobial action of macrophages exposed to hyperoxia. Mouse macrophages were exposed to room air or 95% oxygen for 24 hours, incubated with *Pseudomonas aeruginosa* and after 1 hour, were analyzed for bacterial adhesion, phagocytosis and production of macrophage inflammatory protein (MIP)-1 $\alpha$ . Bacterial adhesion increased 5.8-fold ( $p < 0.0001$ ), phagocytosis was reduced by 60% ( $p < 0.05$ ), and MIP-1 $\alpha$  increased by 49% ( $p < 0.05$ ) in response to hyperoxia. In the presence of the antioxidant enzyme manganese superoxide dismutase (MnSOD) or catalase, bacterial

adhesion was reduced by 30.5%, but only MnSOD significantly improved bacterial phagocytosis and attenuated MIP-1 $\alpha$  production. MnSOD reduced bacterial adhesion and inflammation and improved mononuclear cell bacterial phagocytosis. This mode of action minimizes the development of oxidant-induced pulmonary injury as well as reducing nosocomial infections.<sup>(26)</sup>

### Clinical trials

Supplementation with 150 mg/kg NAC in a bolus followed by 50 mg/kg/day of NAC for 4 days in 27 patients with ALI or ARDS improved the oxygenation rate from the first to the fourth day ( $\text{PaO}_2/\text{FiO}_2$ ,  $440.9 \pm 47.5$  vs.  $151.2 \pm 24.6$ ,  $p < 0.001$ ) and reduced mortality (35.7% vs. 76.9%,  $p = 0.031$ ), but it had no effect on mechanical ventilation time ( $24.8 \pm 8.5$  vs.  $32.9 \pm 9.8$ ,  $p = 0.539$ ).<sup>(19)</sup> These results indicate that intravenous NAC supplementation had beneficial effects on the perfusion-ventilation ratio and a favorable impact on the survival rate. Diets enriched with eicosapentaenoic acid (4.5 g/L), gamma-linolenic acid (4.3 g/L) and antioxidants (320 IU/L vitamin E, 840 mg/L vitamin C and 320 mg/L taurine) had a 0.63 (95% CI 0.39–1.00) relative risk of death. This type of diet also reduced the mechanical ventilation time ( $13.4 \pm 1.2$  vs.  $5.8 \pm 1.0$  days,  $p < 0.001$ ) and length of intensive care unit (ICU) stay ( $10.8 \pm 1.1$  vs.  $4.6 \pm 0.9$ ,  $p < 0.001$ ), and it additionally reduced the number of dysfunctional organs (38% vs. 81%,  $p < 0.001$ ). These results confirm the benefits of antioxidant-enriched diets to ARDS patients but are conflicting in terms of the effects on oxygenation rate ( $156.1 \pm 2.5$  vs.  $158.4 \pm 2.7$ ,  $p \geq 0.05$ ) and mechanical ventilation time.<sup>(20)</sup>

Another benefit of intravenous supplementation (every 8 hours for 10 days) with 70 mg/kg NAC ( $n=14$ ) or 62 mg/kg OTZ-procysteine ( $n=17$ ) was the reduction of the duration of acute lung injury ( $p < 0.05$ ) and the increased cardiac index in both antioxidant treatment groups (NAC/OTZ, 14%; placebo, 6%;  $p < 0.05$ ). However, NAC or OTZ supplementation had no effect on mortality (placebo, 40%; NAC, 36%; OTZ, 35%). This type of therapy may shorten the duration of acute lung injury, but additional studies are necessary to confirm this.<sup>(27)</sup> Nevertheless, the presence of complications (biases), such as reduced consciousness level and feeding-tube or tracheal-tube extubations, may affect the correlations of antioxidant supplementation with oxygenation ratio, mechanical ventilation time, length of hospital stay and mortality

rate. Additionally, these studies evaluated populations above 43 years old that were predominantly comprised of males.

Patients (n=81) receiving 60 IU/L  $\alpha$ -tocopherol and 340 mg/L ascorbic acid through an oro-gastric tube had a relative risk of pulmonary morbidity (a measure composed of ARDS and nosocomial pneumonia) of 0.81 (95% CI 0.60–1.1). Multiple organ failure in patients receiving antioxidant supplementation was significantly lower than in controls (6.1% vs. 2.7%), RR 0.43 (95% CI 0.19–0.96). Early  $\alpha$ -tocopherol and ascorbic acid administration also shortened the length of ICU stay (9 vs. 3 days), RR 0.32 (95% CI 0.09–1.2). Although ascorbic acid and  $\alpha$ -tocopherol supplementation appeared to reduce isoprostane concentration (70.7 vs. 14.8 pg/mL), white blood cell count ( $3.7 \times 10^5$  vs.  $2.7 \times 10^5$ /mL,  $p=0.42$ ), tumor necrosis factor concentration (5.6 vs. 2.7 pg/mL,  $p=0.27$ ), interleukin-1 concentration (23.1 vs. 4.7 pg/mL,  $p=0.26$ ) and interleukin-6 concentration (126.7 vs. 49.9 pg/mL,  $p=0.64$ ), those reductions were not statistically significant. Another notable finding is that supplementation increased interleukin-8 concentration (IL-8, 239.6 vs. 284.4 pg/mL,  $p=0.81$ ), but this increase was not statistically significant.<sup>(28)</sup> These results conflict with previous findings,<sup>(29)</sup> as reduced concentrations of inflammatory markers (isoprostane, IL-1, IL-6 and TNF) could occur even without antioxidant supplementation.

## CLOSING REMARKS

Animal studies show that antioxidant supplementation is associated with the following: better oxygenation rates; higher MPO, ACE, GSH, MnSOD and catalase activities; stronger immune response (reduced isoprostanes, LTB<sub>2</sub>, LTB<sub>4</sub>, IL-1, IL-4 and IL-6); and stronger antibacterial activity (increased monocyte adhesion and macrophage phagocytosis). Additionally, ROS (hydroxyl and hydrogen peroxide), RNS (nitrites and nitrates), and lipid peroxidation (TBARS and MDA) were reduced in both plasma and BALF. In

ALI/ARDS patients, the length of hospital stay, mechanical ventilation time, length of ICU stay, multiple organ dysfunction rate and mortality rate were all reduced. However, the evidence is conflicting regarding the benefits of antioxidant supplementation; therefore, it is not possible to recommend routine antioxidant supplementation in critically ill patients. In future studies, the optimal doses and safest forms of administration of antioxidants should be determined, and later, accurately designed randomized multicenter trials should be conducted to elucidate the effectiveness of antioxidants, either alone or in combination, in treating ALI/ARDS patients.

## RESUMO

**Objetivo:** A pesquisa foi conduzida de maneira a se esclarecer, através de uma meta-análise, as evidências da suplementação de antioxidantes como terapia adjuvante na prevenção dos danos oxidativos e melhora do desfecho clínico, tais como mortalidade, tempo de hospitalização e ventilação mecânica.

**Métodos:** A estratégia de busca de ensaios clínicos randomizados (ECRs) envolveu a participação de dois pesquisadores que avaliaram, de forma independente, a qualidade metodológica de cada artigo, disponível *full text*, nas bases de dados *PubMed*, *ISI of Knowledge e ScienceDirect*.

**Resultados:** Foram extraídos 110 estudos dos últimos 10 anos, porém somente 30 artigos preencheram os critérios metodológicos (ensaios controlados, randomizados, cego e estatisticamente significativo), totalizando 241 animais e 256 pacientes. Este trabalho encontrou um OR de 0,45 [intervalo de confiança (IC) 95%: 0,26 - 0,79] para a mortalidade na comparação do grupo experimental com placebo (6 estudos, n = 256), um OR de 0,46 [intervalo de confiança (IC) 95%: 0,26 - 0,87] para tempo de hospitalização e um OR de 0,63 [intervalo de confiança (IC) 95%: 0,35 - 1,12] para o tempo de ventilação mecânica assistida entre os grupos.

**Conclusão:** As evidências são conflitantes e, desta forma, ainda não é possível recomendar o uso rotineiro da suplementação com antioxidantes em pacientes criticamente enfermos.

**Descritores:** Antioxidantes/uso terapêutico; Lesão pulmonar aguda/quimioterapia; Radicais livres

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