

# Antioxidant (AOX) supplements and clinical course after complex cardiac surgery, major trauma, and subarachnoid haemorrhage



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## Introduction

Critically ill (ICU) patients suffer conditions with increased oxidative stress, which is further increased by some of the treatments used in the ICU. Reactive oxygen species (ROS), despite having beneficial regulatory functions, may be deleterious when their production overwhelms the endogenous antioxidant (AOX) defences, which include vitamins and trace elements. Alteration of endogenous AOX status has been repeatedly described in ICU patients, and particularly in the most severely ill.

Biochemical mechanisms underlying AOX protection are well established: it remains to demonstrate that the AOX reinforcement has beneficial clinical effects. Small size studies have suggested that AOX supplementation may result in clinical benefits after major burns, trauma and sepsis. This study aimed at testing influence of early AOX supplements on organ failure and outcome in a large population of critically ill patients.

## Methods

**Design:** Prospective, randomised, placebo controlled trial in patients admitted to ICU after major cardiac surgery, myocardial infarction, trauma or subarachnoid haemorrhage (SAH).

**Inclusion criteria:** to be critically ill, assessed within 12hrs of admission by the physicians to require more than 48 hrs of ICU

**Exclusion criteria:** absence of consent, burns, liver cirrhosis or hepatic failure grade Child-Puck C.

**Intervention IV :** randomisation to either AOX (Se 270 ug, Zn 20 mg, Vit C 1100 mg, Vit E 310 mg, Vit B<sub>1</sub> 100 mg : double dose on days 1 and 2) or vehicle within 24 hrs of admission, for 5 days. All patients received Vit B<sub>1</sub> 100 mg and Vit C 500 mg bd for 3 days.

### Stratification:

- Cardiac surgery: valves, coronary bypass graft, or combination
- Trauma: ISS <30 or > 30 , Brain injury - yes/no
- Subarachnoidal hemorrhage: 1<sup>st</sup> or 2<sup>nd</sup> admission
- Myocardial infarction

**Outcome variables:** organ failure by SOFA score, length of mechanical ventilation, length of stay in ICU, intermediate care (IC) and hospital (LOS), and outcome (ICU-hospital- 3-month). Acute renal failure was defined by creatinine ↑ of 50 or 90 mmol/l

**Statistics:** Means±SD, One-way ANOVA, Chi square, Wilcoxon, Kaplan-Meier where appropriate. Trends considered at p<0.25, significance at p<0.05.

## Results

205 critically ill patients (median SAPS II=36, probability of death 25%) were enrolled (Table 1). Hospital mortality was 11.2% (23†), while 3-month mortality was 12.7% (26†).

While severity was evenly distributed among cardiac and SAH patients, trauma patients were significantly more severely injured in the AOX group, due to more severe brain injury (ISS-head 14.5 versus 10.9; p=0.02) resulting in more early deaths (6 vs 2: p=0.01). Outcome variables : tables 2 and 3.

Table 2 : Outcome variables – all 205 patients

Variable	Complex cardiac surgery		Trauma		SAH		Myocardial infarction		ALL	
	AOX	P	AOX	P	AOX	P	AOX	P	AOX	P
n	57	56	34	32	11	10	2	3	104	101
Acute RF	29		3		0		0		32	
50†µmol/l	13	16	2	1	-	-	-	-	15	17
Acute RF	15		1		0		0		16	
90†µmol/l	6	9	1	0	-	-	-	-	7	9
Persistent RF	10		1		0		0		11	
	3	7 <sup>1</sup>	1	0	-	-	-	-	4	7
Pneumonia	16		14		0		2		2	
	7	9	7	7	0	0	1	1	1	1
<b>Deaths</b>										
ICU	11		2		0		0		13	
	6	5	2	0 <sup>2</sup>	-	-	-	-	8	5
Hospital	12		8		1		0		23	
	8	6	6	2 <sup>2</sup>	0	1	-	-	14	9
3 months	16		9		1		0		26	
	8	8	7	2 <sup>3</sup>	0	1	-	-	15	11

P value: <sup>1</sup>: =0.17, <sup>2</sup>: =0.16, <sup>3</sup>: p=0.12

Table 3 : Analysis of hospital survivors n=182

Variable	Complex cardiac surgery		Trauma		Subarachnoidal hemorrhage		Myocardial infarction		All survivors	
	AOX	P	AOX	P	AOX	P	AOX	P	AOX	P
n survivors	99	113	58	66	20	21	5	5	182	205
n	49	48	28	30	10	10	2	3	90	92
L.M.Vent	2.3±3.1		4.3±6.3		1.6±2.5		2.1±1.7		2.9±4.4	
	1.9	2.7 <sup>1</sup>	3.8	4.8	1.1	2.2 <sup>2</sup>	2.6	1.8	2.4	3.3 <sup>2</sup>
LICU survivors	4.5±3.9		6.1±6.8		5.4±4.3		4.0±2.3		5.1±5.0	
	4.0	4.6	5.3	6.6	6.0	4.6	4.2	3.8	4.8	5.3
L-IC s	3.9±3.4		6.4±6.5		7.1±5.3		4.0±4.2		5.0±5.0	
	3.5	3.9	7.1	5.9	6.3	8.0	3.0	4.7	4.9	5.2
L-ic+icu s	8.0±4.0		12.5±9.7		12.4±6.9		8.0±4.0		10.1±7.5	
	7.7	8.3 <sup>3</sup>	12.5	12.5	12.3	12.6	7.2	8.5	9.7	10.5
LOS s	19.3±13.5		34.3±22.9		27.3±29.8		31.0±32.8		25.1±20.1	
	19	19	29.2	39.6 <sup>4</sup>	31.7	21.9	17.5	41	23.7	26.6

P value: <sup>1</sup>: =0.19, <sup>2</sup>: p=0.15, <sup>3</sup>: =0.2, <sup>4</sup>: =0.09

Abbreviations: IC = intermediate care, LOS= length hospital stay, RF = renal failure

Table 1 : Patient characteristics

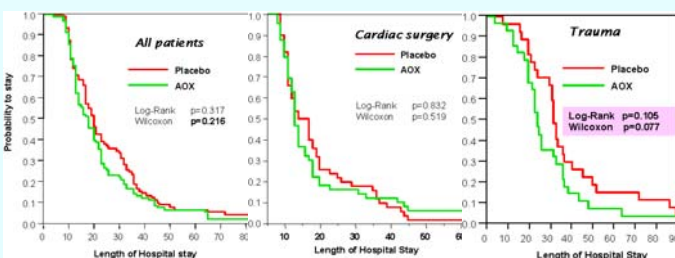
Variable	Complex cardiac surgery		Trauma		Subarachnoidal hemorrhage		Myocardial infarction		ALL	
	AOX	P	AOX	P	AOX	P	AOX	P	AOX	P
n	113		66		21		5		205	
	57	56	34	32	11	10	2	3	104	101
Age	70.2±10.4 <sup>1</sup>		40.0±18.6 <sup>1</sup>		53.6±8.7		68.2±10.8		58.7±19.2	
	69	71.1	40	40	54	53	67	69	58	60
Sex	70 M / 43 F		52 M / 14 F <sup>1</sup>		5 M / 16 F <sup>1</sup>		3 M / 2 F		129 M / 76 F	
	37/19	33/24	26/8	26/6	2/8	3/8	2/1	1/1	63/41	66/35
SAPS II	39.3±10.4		35.7±15.4		33.9±13.6		41.0±10.9		37.6±12.7	
	38.4	40.3	39.9	31.1 <sup>2</sup>	33.6	34.2	43	41	38.4	36.8
BMI	26.5±5.0		24.9±3.9		24.5±3.4		24.7±3.9		25.7±4.6	
	26.7	26.2	24.2	25.6	25.2	23.7	24.1	25.0	25.7	25.7
SOFA	9.1±1.7 <sup>1</sup>		7.5±3.1		6.3±2.9		7.8±2.6		8.2±2.5	
adm	8.8	9.3	7.8	7.1	5.7	6.9	7.5	7.8	8.1	8.3
SOFA	9.0±2.2 <sup>1</sup>		7.2±3.2		6.7±3.1		7.0±3.1		8.2±2.8	
worst	8.7	9.3 <sup>2</sup>	4.5	6.9	6.6	6.8	5.5	8.0	8.1	8.2

P value: <sup>1</sup>: < 0.001, <sup>2</sup>: 0.18, <sup>3</sup>: =0.01

## References

1. Heyland DK, et al: Antioxidant nutrients: A systematic review of trace elements and vitamins in the critically ill. *Intensive Care Med* 2005; 31:321-337
2. Moreno R, et al: The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. *Intensive Care Med* 1999; 25:686-696
3. Mehta RL & Chertow GM: Acute renal failure definitions and classification: Time for change? *J Am Soc Nephrol* 2003; 14:2178-2187

Figure 1: Length of hospital stay in survivors: all, cardiac and trauma patients – near significance in trauma patients



## Conclusion

AOX supplements containing selenium and delivered for 5 days after ICU admission were associated with trends to lower incidence of acute renal failure and shorter hospital stay in critically ill cardiac surgery and trauma patients. Cardiac surgery and trauma patients appeared best candidates for AOX intervention.

But despite the enrollment of 205 patients, the power was still insufficient to achieve significant differences. Analysis of confounding factors (energy delivery, glucose control) is ongoing.