



Abstract title: Reversal of oxidative stress by antioxidant therapy improves routine and advanced sperm functions

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Study question: Can supplementation with antioxidants reverse a seminal oxidative stress (OS) state?

Summary answer: Antioxidants can be used to treat seminal OS with subsequent significant improvements in conventional semen parameters and sperm DNA fragmentation (SDF) levels.

What is known already: OS has been recognized as an important cause of male factor infertility. It can trigger sperm lipid peroxidation, DNA fragmentation and abortive apoptosis. Oxidation reduction potential (ORP) measures the balance between oxidants and reductants in a given medium. While various measures of OS have been used to examine the effect of antioxidant treatment, ORP has not been particularly investigated. An ORP reference value of 1.38 mvolts/10⁶ sperm has been reported previously to discriminate between abnormal and normal semen quality.

Study design, size, duration: This was a prospective study conducted in a tertiary medical centre between January to June 2018 including 148 patients presenting with male infertility of >1year duration, at least one abnormal semen parameter and documented normal female partner fertility. Patients with varicocele, leukocytospermia, genitourinary infections, any febrile illness in the past 6 months and exposure to chemo-radiation were excluded from this study. Patients with seminal OS detected by a high ORP level were included in this analysis.

Participants/materials, setting, methods: All participants were treated with the antioxidant supplement FH PRO (Fairhaven Health, Bellingham, WA) for a period of 3 months. Semen analysis, SDF (sperm chromatin dispersion test) and ORP (MiOXSYS, Aytu BioScience, Englewood, CO) tests were performed initially and immediately following treatment. Results were compared using Kruskal Wallis Test and a p value of <0.05 was considered statistically significant. The SPSS version 20 (IBM, Armonk, NY) was used to conduct the statistical analysis.

Main results and the role of chance: A total of 116 participants with high ORP value of 12.84 ± 1.6 mVolts/10⁶ sperm were included in this analysis. The study participants' mean age and body mass index were 36.3 ± 0.6 years and 29.8 ± 0.43 Kg/m² respectively. Following treatment, the ORP level decreased significantly in 99/116 (85.3%) but were normalized in only 41/116 (35%) patients. Overall, significant improvements were noted in sperm concentration (+9.02 ± 1.41 x10⁶/ml, p<0.001), total motility (+3.97 ± 1.59%, p=0.013), progressive motility (+3.31 ± 0.79%, p<0.001), normal morphology (+1.09 ± 1.99 %, p<0.001) and SDF (-6.03 ± 1.99%, p=0.004). Patients with normalized ORP levels following treatment had better improvements in conventional semen parameters and SDF values than patients in whom the ORP level improved but remained abnormal (Table 1). These differences were statistically significant only for conventional semen parameters.

Variable	Normal ORP post treatment (n=41)	Abnormal ORP post treatment (n=58)	P value*
Semen Volume (ml)	-0.04±0.17	-0.27±0.18	0.572
Sperm Count (10 ⁶ /ml)	+21.52±2.15	+3.49±1.2	<0.001
Total Motility (%)	+12.54±2.56	+1.2±2.09	0.001
Progressive Motility (%)	+7.90±1.42	+1.72±0.95	<0.001
Normal Morphology (%)	+2.19±0.48	+0.82±0.26	0.017
SDF (%)	-8.19±2.5	-5.03±3.33	0.508

Limitations, reasons for caution: The study lacked a placebo group which could be considered as one limitation.

Wider implications of the findings: Antioxidant supplements can reverse the seminal OS state and in turn improve semen parameters and SDF levels. These improvements are expected to hold a favorable effect on the male's fertility potential.

Trial registration number: 16351/16