


A Meta-Analysis of the Efficacy of L-Carnitine/L-Acetyl-Carnitine or N-Acetyl-Cysteine in Men With Idiopathic Asthenozoospermia

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Abstract

The meta-analysis was performed to access efficacy of L-carnitine/L-acetyl-carnitine (LC/LAC) and N-acetyl-cysteine (NAC) in men with idiopathic asthenozoospermia. We researched PubMed, EMBASE, and Cochrane Library databases and references to related articles. Finally, seven articles including 621 patients were analyzed. The results indicated that LC/LAC and NAC had a considerable improvement in sperm motility ($p = .03$ and $p < .0001$, respectively) and normal morphology ($p = .006$, $p = .0002$, respectively) compared with the placebo group. Besides, NAC had a significantly greater increase in sperm concentration ($p < .00001$) and ejaculate volume ($p = .002$) compared with the placebo group, and there was no significant difference in LC/LAC. For the analysis of serum hormones, NAC had no obvious differences in improving the serum testosterone, luteinizing hormone, follicle-stimulating hormone, and prolactin compared with non-treatment group. Conclusively, LC/LAC and NAC showed a greater improvement in sperm motility and normal morphology. Moreover, NAC has a positive effect on sperm concentration and ejaculate volume, whereas no obvious effect was observed in serum hormones.

Keywords

L-carnitine, L-acetyl-carnitine, N-acetyl-cysteine, meta-analysis, idiopathic asthenozoospermia

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It is reported that about half of childless couples with infertility are not pregnant due to male factors (Gnoth et al., 2005). Among them, 44% of infertile men had no known disease that could explain infertility and these patients were assigned as idiopathic male infertility (Pierik et al., 2000). As the pathogenesis of this disease is not completely clear, there is no evidence-based treatment for idiopathic male infertility, and most treatments depend on clinical experience (Dohle et al., 2012).

L-carnitine (LC) plays an important role in cellular energetic metabolism, and it acts as a shuttle of the acyl-CoA into the mitochondria (Bremer, 1983; Jeulin et al., 1994). High levels of LC in epididymal fluid plays an important role in sperm cell metabolism (Enomoto et al., 2002), and some studies report that the onset of sperm motility is related to the increase of LC in epididymal cavity and the concentration of L-acetyl-carnitine (LAC) in

sperm cells (Radigue et al., 1996). N-acetyl-cysteine (NAC) as a derivative of L-cysteine is frequently regarded as antioxidant (Zafarullah et al., 2003). It was reported that NAC has the function of scavenging free radicals in vivo and in vitro (Ciftci et al., 2009; Erkkilä et al., 1998; Oeda

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et al., 1997). Compared with placebo, NAC orally daily can significantly improve sperm motility (Safarinejad & Safarinejad, 2009). Moreover, NAC can not only increase sperm concentration and acrosome reaction but also reduce reactive oxygen species (ROS) and sperm DNA oxidation (Comhaire et al., 2000).

The efficacy of LC / LAC and NAC in the treatment of idiopathic asthenospermia has not been evaluated by evidence-based medicine (EBM). Therefore, a meta-analysis was carried out.

Materials and Methods

Protocol

This meta-analysis strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) list (Moher et al., 2010).

Literature Sources and Search Strategy

Two reviewers searched independently for all randomized controlled trials (RCTs) published until August 31, 2020, involving the efficacy of LC/LAC and NAC in men with idiopathic asthenozoospermia. They researched PubMed, EMBASE, and Cochrane Library databases and references of the included studies; Medical Subject Headings (MeSH) terms were “L-carnitine, L-acetyl-carnitine, N-acetyl-cysteine, NAC, LC, LAC, infertile, idiopathic, idiopathic infertile, men, male, idiopathic asthenozoospermia.”

Inclusion and Exclusion Criteria

Inclusion criteria: there are no identifiable medical conditions that could explain infertility and these cases are classified as idiopathic male infertility—this study only included patients with idiopathic male infertility; LC/LAC and NAC in treating men with idiopathic asthenozoospermia were evaluated; full text available; data including the number of participants and the vary of each indicator; RCT. Exclusion criteria: not RCT, such as abstract, review, or comment; patients with urogenital bacterial infection, smoke, hypogonadism, varicocele and other comorbidities; other treatment. The PRISMA flowchart is illustrated in Figure 1.

Quality of Assessment

The quality of RCTs was accessed using the Cochrane Handbook for Systematic Reviews of Interventions v.5.3.0 (Cumpston et al., 2019). The RCTs were classified using the same Handbook (Cumpston et al., 2019). Three quality classification criteria: (+) RCT would be

considered a low possibility of bias for conforming to almost all quality criteria; (?) RCT would be counted a secondary probability for fulfilling partial quality criteria or indistinct; (-) RCT would be considered a high possibility of bias for conforming to bare quality criteria.

Data Extraction

The relevant data are extracted as follows: characteristics of study; name of authors; study design and sample size; interventions among the groups; and evaluation index, such as sperm concentration, ejaculate volume, sperm motility, normal morphology, testosterone, luteinizing hormone, follicle-stimulating hormone, and prolactin. All authors checked the accuracy of the data. In addition, this research did not require ethical consent.

Statistical Analysis

Rev man 5.3.0 was used to analyze the data. Mean difference (MD) with 95% confidence interval (CI) was used to evaluate continuous index, and odds ratio (OR) with 95% CI was used to evaluate dichotomous index. The fixed effect model was used and considered to be homogeneous, if the result was $p > .05$ (DerSimonian & Laird, 1986). I^2 statistic was applied to analyze inconsistent results. Random effect model was adopted when the index showed $p < .05$ or $I^2 > 50\%$. If the result showed $p < .05$, the results were considered statistically significant.

Results

Basic Characteristics and Search Process

The reviewers searched 219 studies in three databases. According to the inclusion criteria, 184 studies were excluded. Due to the lack of valid data, 28 studies were excluded. At last, seven RCTs (Ciftci et al., 2009; Jannatifar et al., 2019; Kopets et al., 2020; Lenzi et al., 2004; Micic et al., 2019; Safarinejad & Safarinejad, 2009; Sigman et al., 2006) were used to show the efficacy of LC/LAC and NAC in men with idiopathic asthenozoospermia. Table 1 presents the basic characteristics of each study.

The Risk of Bias in Included Literature

All included studies were randomized controlled design with specific randomized protocols, and three study described the calculation of sample size. The outcomes of quality assessment are presented in Table 2. The risk of bias graph is presented in Figure 2.

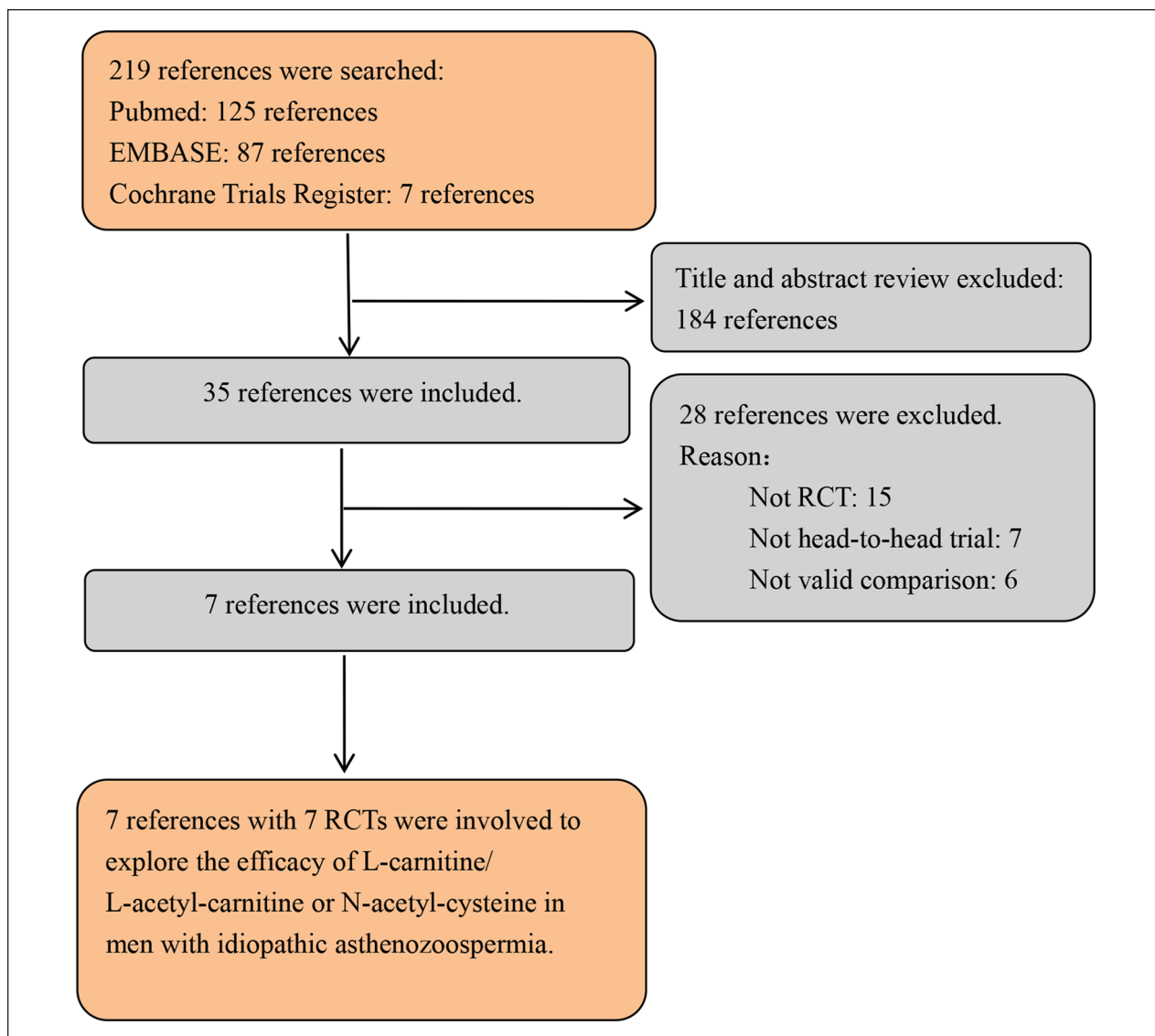


Figure 1. Flowchart of selection PRISMA.

Note. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs = randomized controlled trials.

Sperm Concentration

LC/LAC Versus Placebo. Four RCTs including 190 patients were included in the analysis. Forest plots drew an MD of $11.17 \times 10^6/\text{mL}$ and 95% CI $[-7.85, 30.20]$ ($p = .25$), which indicated that LC/LAC did not have a better effect in raising sperm concentration compared with the placebo (Figure 3).

NAC Versus Placebo. Three RCTs including 431 patients were included in the analysis. Forest plots drew an MD of $3.80 \times 10^6/\text{mL}$ and 95% CI $[2.36, 5.24]$ ($p < .00001$), which indicated that NAC had a significantly greater

increase in sperm concentration compared with the placebo (Figure 3).

Sperm Volume

LC/LAC Versus Placebo. Two RCTs including 86 patients were included in the analysis. Forest plots drew an MD of 11.17 mL and 95% CI $[-7.85, 30.20]$ ($p = .25$), which indicated that LC/LAC did not have a better effect in raising sperm volume compared with the placebo (Figure 4).

NAC Versus Placebo. Three RCTs including 431 patients were included in the analysis. Forest plots drew an MD of

Table 1. The Details of Individual Studies.

Study	Country	Study Design	Treatment		Sample Size		Follow-Up	Dose	Mode of Administration	Inclusion Criteria
			Experimental	Control	Experimental	Control				
Kopets et al. (2020)	Ukraine	Randomized controlled trial	LC/LAC	Placebo	42	41	4 months	1990 mg daily	Oral	Age 21–50 years, idiopathic male infertility defined as absence of conception in a couple having a regular unprotected intercourse for 12 months with a woman without evident pathology that could cause infertility, sperm concentration <15 million/mL and/or <32% forms with progressive motility and/or <4% of sperm cells with normal morphology. Age 20–40 years, infertility \geq 2 years after regular sexual intercourses with a fertile woman; normal rheologic characteristics (appearance, consistency, and liquefaction) of semen, and volume and pH in the normal range; sperm count 20×10^6 /mL, sperm motility <50%, and normal sperm morphologic features \geq 30%.
Balercia et al. (2005)	Italy	Randomized controlled trial	LC/LAC	Placebo	15	15	6 months	2 g/l g daily	Oral	Males aged 18–65 years with infertility of at least 6 months duration, sperm concentration of at least five million sperm/mL, motility of 10%–50%. Normal rheological characteristics (appearance, consistency, and liquefaction), volume and pH in the normal range, sperm concentration of $10\text{--}40 \times 10^6$ /mL; forward motility, <15%; total motility, 10%–40%; atypical forms, <80%; semen leukocytes, < 1×10^6 /mL.
Sigman et al. (2006)	USA	Randomized controlled trial	LC/LAC	Placebo	12	9	6 months	2 g/l g daily	Oral	Sperm count $\geq 5 \times 10^6$ /mL, no factors in their history with a possible influence for male infertility, \geq 2 years of failed attempts at conception, no female factors.
Lenzi et al. (2004)	Italy	Randomized controlled trial	LC/LAC	Placebo	30	26	6 months	2 g/l g daily	Oral	Idiopathic infertility with normal sperm parameters, determined by medical history and physical and seminal examination findings.
Safarinejad & Safarinejad (2009)	Iran	Randomized controlled trial	NAC	Placebo	105	106	26 weeks	600 mg daily	Oral	The infertile couples with no previous report of pregnancy, normal female partner, and male partner defined as having asthenoteratozoospermia.
Ciftci et al. (2009)	Turkey	Randomized controlled trial	NAC	Placebo	60	60	3 months	600 mg daily	Oral	
Jannatifar et al. (2019)	Iran	Randomized controlled trial	NAC	Placebo	50	50	3 months	600 mg daily	Oral	

Note. LC/LAC = L-carnitine/L-acetyl-carnitine; NAC = N-acetyl-cysteine.

Table 2. The Quality Assessment of Each Study.

Study	Random Sequence Generation (Selection Bias)		Allocation Concealment (Selection Bias)		Blinding of Participants and Personnel (Performance Bias)		Blinding of Outcome Assessment (Detection Bias)		Incomplete Outcome Data (Attrition Bias)		Selective Reporting (Reporting Bias)		Other Bias		Calculation of Sample Size	Statistical Analysis
	+	-	+	-	+	-	+	-	+	-	+	-	+	-		
Kopets et al. (2020)	+		+		+		+		+		+		+		Yes	ANCOVA
Balercia et al. (2005)	+		+		+		+		+		+		+		No	ANCOVA
Sigman et al. (2006)	+		+		+		+		+		+		+		No	Friedman test
Lenzi et al. (2004)	+		+		+		+		+		+		+		Yes	Independent-samples test; Student's t-test; ANOVA; Mann-Whitney U test
Safarinejad & Safarinejad (2009)	+		+		+		+		+		+		+		Yes	ANOVA; Mann-Whitney U test
Ciftci et al. (2009)	+		+		?		?		+		-		+		No	Whitney U test
Jannatifar et al. (2019)	+		+		+		+		+		+		+		No	Student's t-test

Note. ANCOVA = analysis of covariance.

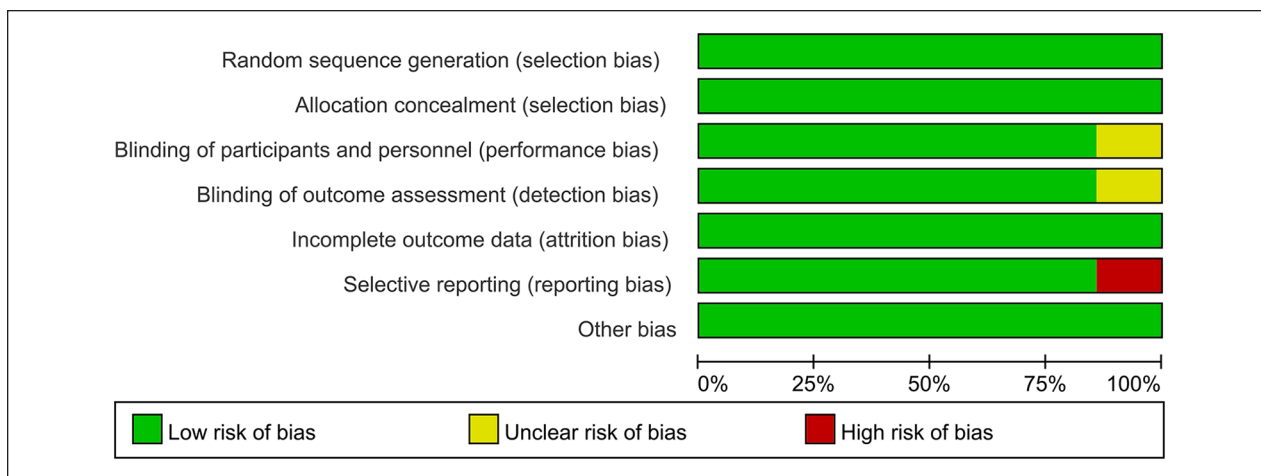


Figure 2. The risk of bias graph.

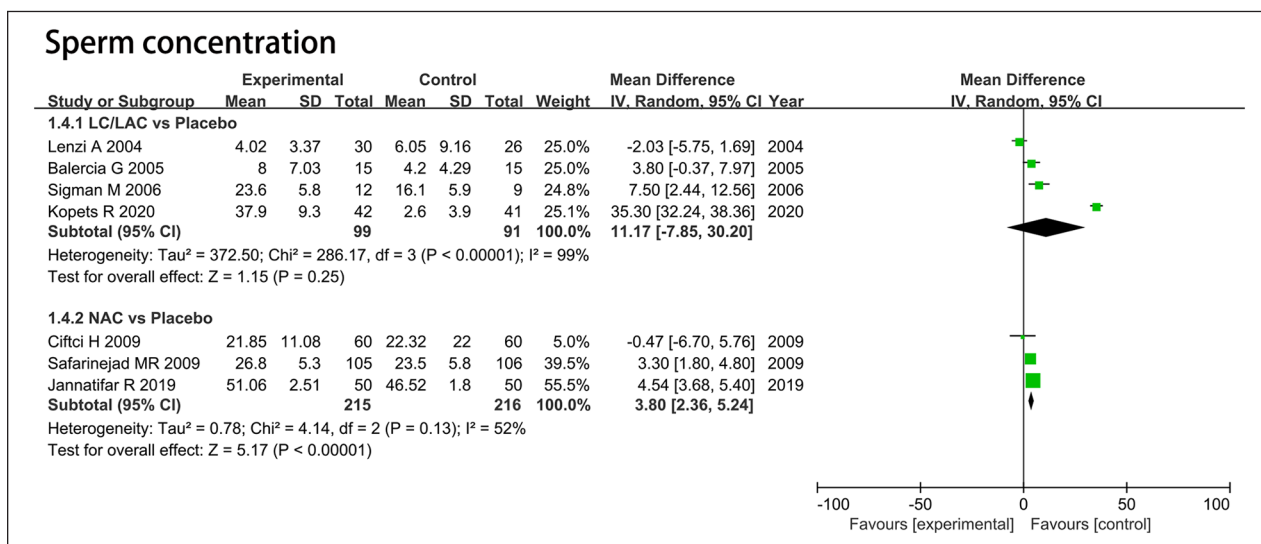


Figure 3. Forest plots showing results in sperm parameters on the sperm concentration.

Note. SD = standard deviation; IV = inverse variance; CI = confidence interval; df = degrees of freedom.

0.69 ml and 95% CI [0.26, 1.12] ($p = .002$), which indicated that NAC had a significantly greater increase in sperm volume compared with the placebo (Figure 4).

Sperm Motility (%)

LC/LAC Versus Placebo. Four RCTs including 190 patients were included in the analysis. Forest plots drew an MD of 9.48 and 95% CI [0.95, 18.01] ($p = 0.03$), which indicated that LC/LAC had a better effect in raising sperm motility compared with the placebo (Figure 5).

NAC Versus Placebo. Three RCTs including 431 patients were included in the analysis. Forest plots drew an MD of

4.69 and 95% CI [2.45, 6.94] ($p < .0001$), which indicated that NAC had a significantly greater increase in sperm motility compared with the placebo (Figure 5).

Normal Morphology (%)

LC/LAC Versus Placebo. Two RCTs including 139 patients were included in the analysis. Forest plots drew an MD of 4.89 and 95% CI [1.40, 8.39] ($p = .006$), which indicated that LC/LAC had a better effect in raising normal morphology compared with the placebo (Figure 6).

NAC Versus Placebo. Three RCTs including 431 patients were included in the analysis. Forest plots drew an MD of

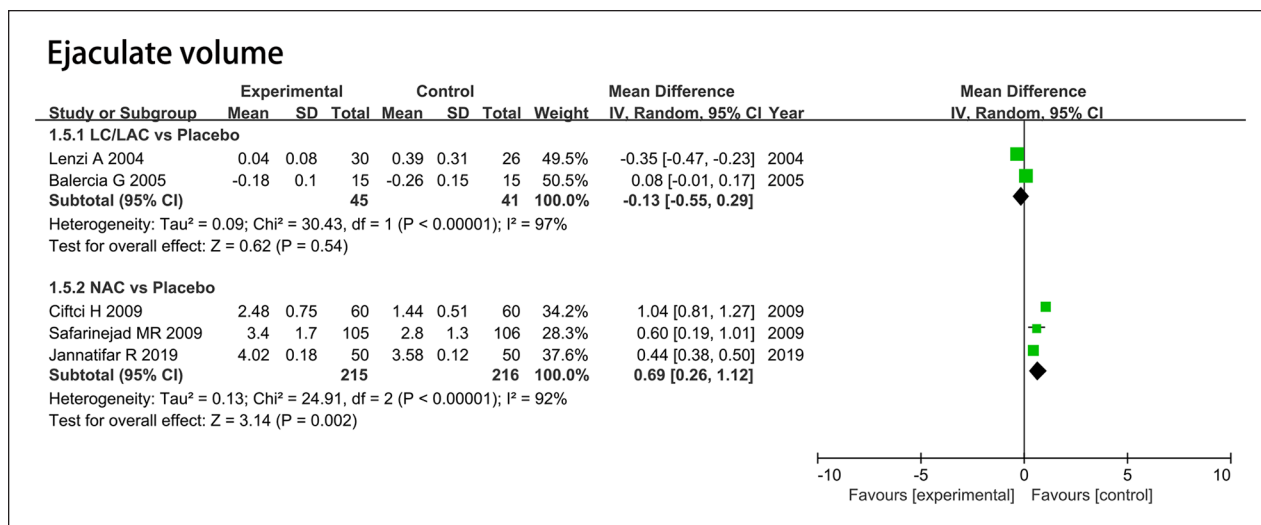


Figure 4. Forest plots showing results in sperm parameters on the sperm volume.
 Note. SD = standard deviation; IV = inverse variance; CI = confidence interval; df = degrees of freedom.

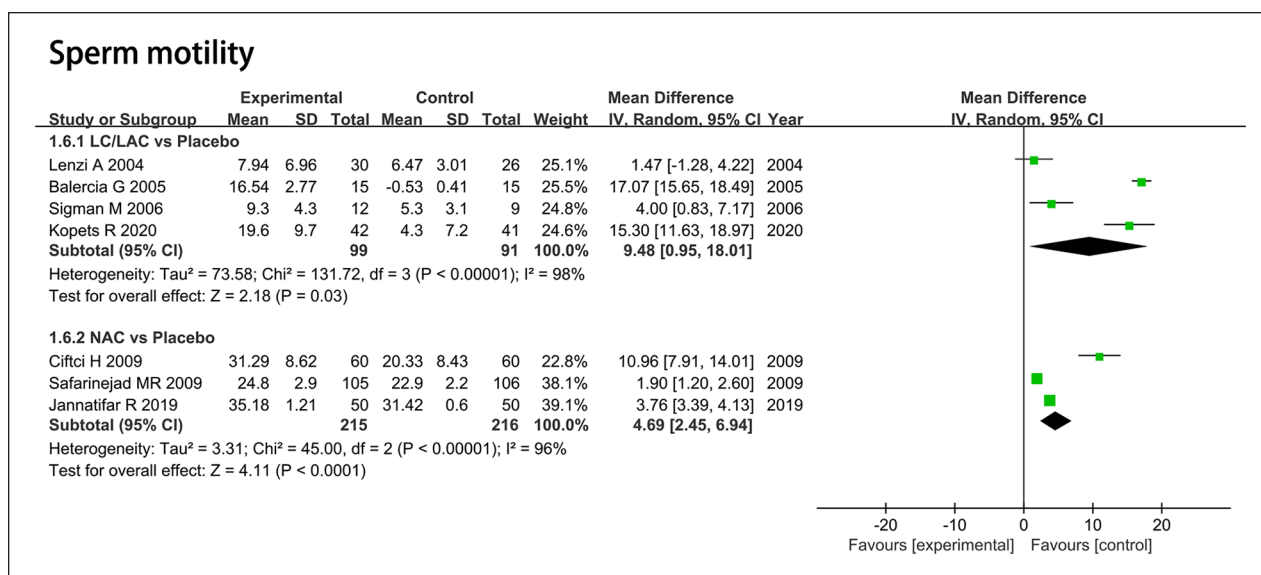


Figure 5. Forest plots showing results in sperm parameters on the sperm motility.
 Note. SD = standard deviation; IV = inverse variance; CI = confidence interval; df = degrees of freedom.

1.68 and 95% CI [0.79, 2.58] ($p = .0002$), which indicated that NAC had a significantly greater increase in normal morphology for infertile men compared with the placebo (Figure 6).

Hormonal Analysis

Two RCTs including 311 patients (155 patients in the NAC group and 156 patients in the placebo group) were used to estimate the level of testosterone, luteinizing

hormone, follicle-stimulating hormone, and prolactin. The random model showed that there were no significant differences between NAC and placebo in raising the level of testosterone (MD, 1.35 ng/mL; 95% CI [-0.75, 3.45]; $p = .21$; Figure 7), luteinizing hormone (MD, 0.82 mIU/mL; 95% CI [-1.07, 2.71]; $p = .40$; Figure 7), follicle-stimulating hormone (MD, -7.48 mIU/mL; 95% CI [-21.23, 6.27]; $p = .29$; Figure 7), and prolactin (MD, -0.34 ng/mL; 95% CI [-1.02, 0.33]; $p = .32$; Figure 7) for infertile men compared with the placebo.

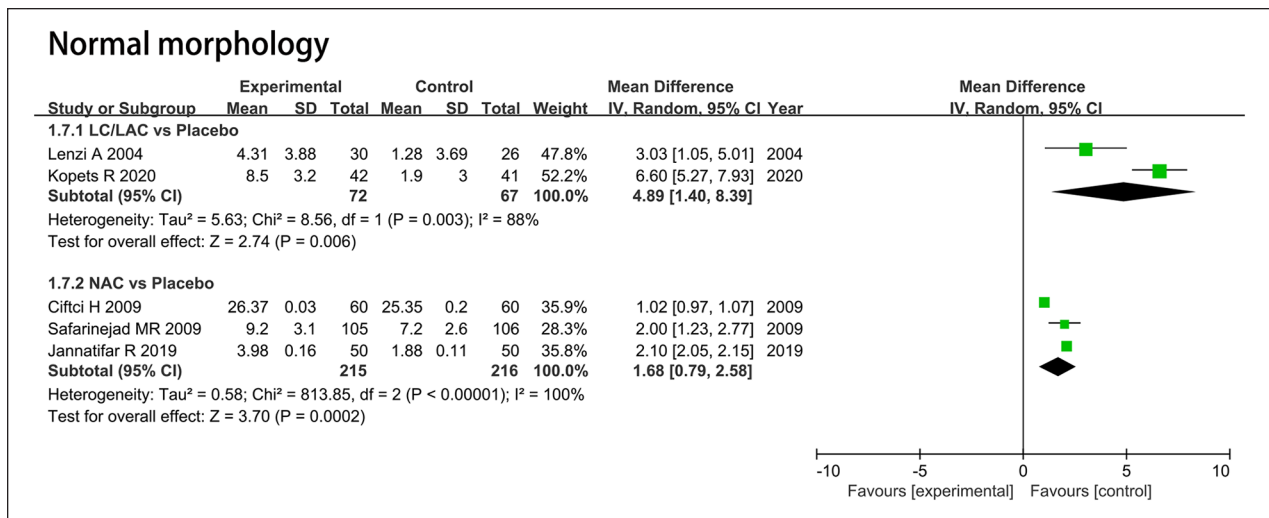


Figure 6. Forest plots showing results in sperm parameters on the normal morphology.

Note. SD = standard deviation; IV = inverse variance; CI = confidence interval; df = degrees of freedom.

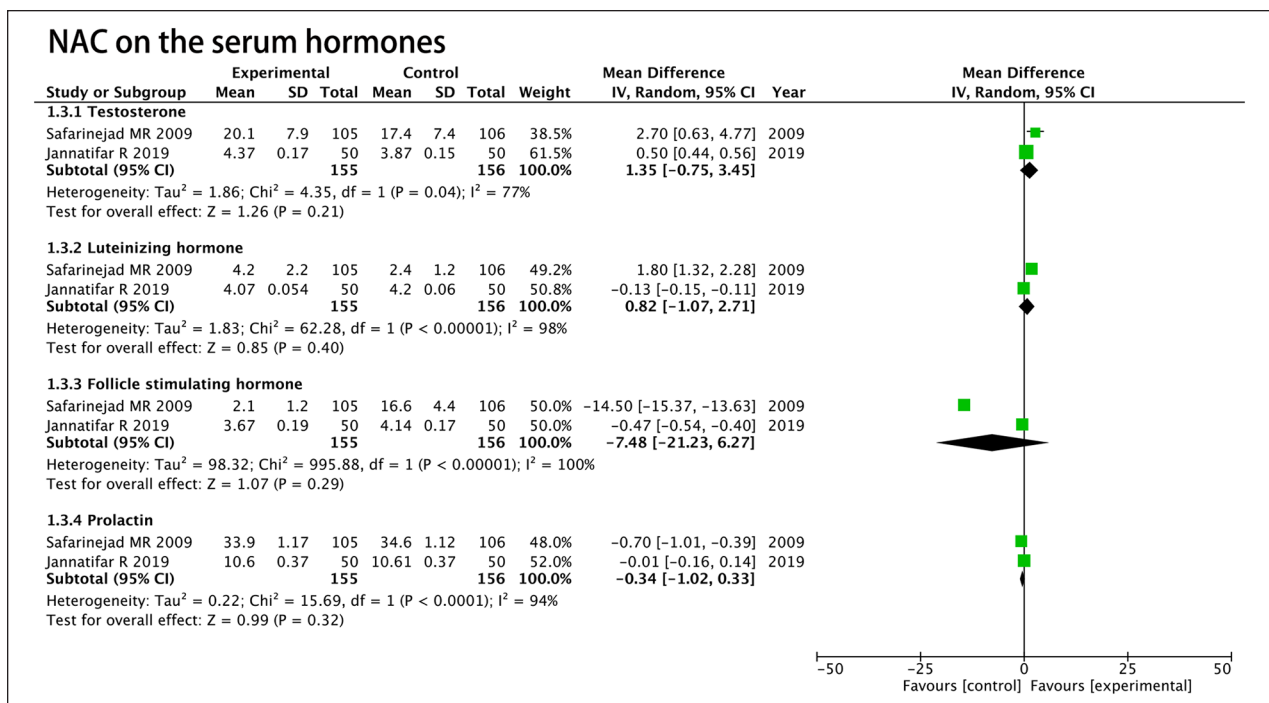


Figure 7. Forest plots showing results in hormonal analysis.

Note. SD = standard deviation; IV = inverse variance; CI = confidence interval; df = degrees of freedom.

Discussion

This meta-analysis aimed to confirm the efficacy of LC/LAC and NAC in men with idiopathic asthenozoospermia from the perspective of EBM. The results indicated that LC/LAC and NAC had a considerable improvement in sperm motility and normal morphology compared with the placebo group. Besides, NAC had a significantly

greater increase in sperm concentration and ejaculate volume compared with the placebo group, and there was no significant difference in LC/LAC. For the analysis of serum hormones, NAC had no obvious differences in improving the serum levels of testosterone, luteinizing hormone, follicle-stimulating hormone, and prolactin compared with the placebo group.

Infertility is an important medical and social problem, which has a huge impact on health (Agarwal et al., 2020). Among them, the treatment of idiopathic male infertility is still controversial, and most of the clinical treatment still depends on empirical methods (Agarwal et al., 2020). In recent years, the application of LC/LAC in the treatment of oligoasthenoteratozoospermia of unknown origin has been proposed. Many studies have reported that their effects on sperm epididymal maturation and energy metabolism are an intracellular mechanism, and their effects on testicular epididymal microenvironment are an indirect antioxidant effect (Lenzi et al., 1992).

Free LC, named 3-hydroxy-4-N-trymethylaminobutyric acid, plays a key role in cell energy production. Free LC is a necessary molecule in the process of mitochondrial oxidation of long chain fatty acids. Fatty acids must combine with coenzyme A (CoA) to form acyl-CoA to enter the mitochondria. Long chain acyl-CoA can't pass through the internal mitochondrial membrane, and hence this progress needs a specific enzymatic mechanism, which uses LC as a shuttle (Bremer, 1983; Jeulin et al., 1994; Jeulin & Lewin, 1996). After transport into the mitochondria, acyl is transferred to the mitochondrial CoA by acyl-carnitine. This initiates oxidation with the product adenosine triphosphate and finally exits as LAC to start a new transport cycle. Carnitine can not only protect cell membrane and DNA from oxygen free radical damage but can also prevent protein oxidation and pyruvate and lactate oxidative damage (Arduini, 1992). The activation of sperm motility occurred simultaneously with the increase of carnitine concentration in the epididymal lumen and LAC in the spermatozoa (Radigue et al., 1996). Epididymal epithelium secretes LC into the lumen through a specific active transport system (Enomoto et al., 2002). Considering their mechanisms and functions, LC and LAC have been proposed as a possible treatment in selected forms of oligoasthenoteratozoospermia (Lenzi et al., 2003; Vicari et al., 2002).

NAC is a N-acetyl derivative of natural amino acid L-cysteine. Because it can significantly reduce disulfide bond, NAC is used to reduce viscosity and elasticity of mucus (Aitken et al., 1993). Like many thiols, NAC is a good scavenger for hydroxyl radicals (Orzechowski et al., 2002). In the included literature, all patients were treated with 600 mg/d NAC for at least 3 months, which was considered as a safe drug dose with a higher median lethal dose (Ciftei et al., 2009; Jannatifar et al., 2019; Safarinejad & Safarinejad, 2009). The study reported that although sperm density and sperm activity did not improve, sperm function tended to improve and ROS level decreased significantly after NAC administration (Akiyama, 1999). Different from the results of this study, an RCT found that sperm motility was improved after NAC treatment. In this meta-analysis, compared with the

control group, the viscosity, liquefaction time, and sperm volume of NAC group were significantly increased.

It is found that semen mucinosis is closely related to male infertility (Elzanaty et al., 2004). Semen viscosity plays an important role in the process of pregnancy because the sperm may adhere to semen fiber or mucus, which prevents the sperm from migrating from seminal plasma to the cervix and fertilization site. NAC can reduce the effect of ROS activity in the sperm, which was a factor for reducing sperm viscosity (Orzechowski et al., 2002).

This study reported the positive effects of the use of the LC/LAC and NAC for treating male infertility caused by oxidative stress on the semen parameters. The latest report stated that administrating the exogenous antioxidants can cause oxidative stress induced by the antioxidant paradox or reductive stress accompanied by diminishments in the endogenous oxidants, which are required to induce the physiological pathways that suppress functions like sperm capacitation (Beygi et al., 2020). Thus, these antioxidants should be received cautiously and patients should take necessary tests for their redox status prior to the treatment with a supplement of specific formulation. Notably, the treatment should be specifically personalized to achieve normal redox status (Henkel et al., 2019).

Spermatogenesis is highly controlled by hormonal environment, in addition to affecting the speed and quality of spermatogenesis; any change of hormone distribution may profoundly affect the chromosome ploidy and the integrity of sperm chromatin (Safarinejad & Safarinejad, 2009). The increase of testosterone has a negative feedback effect on the secretion of hypothalamus and pituitary, which leads to the decrease of GnRH pulse frequency and pituitary response to GnRH, and finally the decrease of gonadotropin release (Hayes et al., 2000). Khan et al. (2013) reported that the level of total antioxidant capacity (TAC) in seminal plasma of patients with asthenospermia was significantly lower than that of healthy men. Jannatifar et al. (2019) reported that the concentration of seminal malondialdehyde (MDA) decreased significantly, and MDA was a specific marker of lipid peroxidation, while TAC increased significantly after NAC treatment. Therefore, NAC reduces the severity of oxidative stress, thus reducing lipid peroxidation and DNA fragmentation.

We need to acknowledge the limitations of this analysis. There are deficiencies in the quality of the trials used for analysis, mainly including fewer trials included and inconsistent basic indicators of various studies. However, the studies included in this study are all RCTs, which increases the strength of the research results. In addition, selection bias and subjective bias may affect the final results of this study.

Conclusions

LC/LAC and NAC showed a greater improvement in sperm motility and normal morphology. Moreover, NAC has a positive effect on sperm concentration and ejaculate volume, whereas no obvious effect in serum hormones.

Author Contribution

Conceptualization: Yong Zhang. Data curation: Guangzhu Wei, Zhongbao Zhou, Yuanshan Cui. Formal analysis: Guangzhu Wei, Zhongbao Zhou. Funding acquisition: Yong Zhang, Yuanshan Cui. Investigation: Yongjin Huang, Zijin Wan, Xuanyan Che, Yumeng Cai. Methodology: Guangzhu Wei, Zhongbao Zhou, Yongjin Huang, Zijin Wan, Xuanyan Che. Project administration: Yong Zhang. Resources: Zijin Wan, Xuanyan Che, Yumeng Cai. Software: Guangzhu Wei, Zhongbao Zhou. Supervision: Yong Zhang. Writing – original draft: Guangzhu Wei, Yuanshan Cui, Yongjin Huang. Writing – review & editing: Yong Zhang, Yuanshan Cui.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical statement

No ethics to disclose.

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