SYSTEMATIC REVIEW

The use of N-acetylcysteine to prevent further progression of preeclampsia

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ABSTRACT

Objective: Preeclampsia is a prevalent disorder among pregnant women, characterized by hypertension and proteinuria, leading to serious complications. However, the precise pathophysiology of preeclampsia remains debated. Oxidative stress is believed to play a significant role in its development, and N-acetylcysteine (NAC) is known to influence this pathway. NAC aids in glutathione synthesis, a critical antioxidant, and acts as a free radical scavenger. This study aimed to examine the role of NAC in women with preeclampsia, focusing on its potential therapeutic benefits.

Materials and Methods: A comprehensive literature search was conducted using PubMed and ScienceDirect databases, yielding 17 articles from PubMed and 395 articles from ScienceDirect. Reviews were excluded, resulting in 12 articles from PubMed and 89 articles from ScienceDirect. After further screening, 5 articles were selected for review, including 2 human studies and 3 animal studies, to understand the impact of NAC on preeclampsia.

Results: Human studies indicated that NAC supplementation reduced the rate of preeclampsia among women at increased risk. Animal studies supported these findings, showing improvements in oxidative stress biomarkers, laboratory values, and blood pressure in models treated with NAC. NAC supplementation was associated with positive outcomes in managing oxidative stress, a key factor in the pathogenesis of preeclampsia.

Conclusion: NAC supplementation in women with preexisting preeclampsia has beneficial effects on oxidative stress biomarkers, laboratory values, and blood pressure. These highlight the potential of NAC as a therapeutic intervention for preeclampsia, particularly in women at high risk. However, no significant differences were observed in maternal complication rate between the NAC-treated group and the control group. Further research is needed to fully understand the clinical implications of NAC supplementation and its long-term safety and efficacy in managing preeclampsia.

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Highlights:

1. The generation of free radicals in the placenta leads to endothelial dysfunction, which contributes greatly in preeclampsia.
2. N-acetylcysteine have a role in the oxidative stress pathway, helping in glutathione synthesis and as a free radical scavenger.
3. N-acetylcysteine supplementation in women with preexisting preeclampsia had positive effects on oxidative stress biomarkers, laboratory values, and blood pressure.

INTRODUCTION

Preeclampsia is a very common disorder, associated with high numbers of both maternal and fetal morbidity and mortality.[1,2] The pathophysiology of preeclampsia remains in academic debate, but one such theory states that the generation of free radicals in the placenta leads to endothelial dysfunction, which contributes greatly in preeclampsia.[3] As such, the use of antioxidants became one such promising endeavor in combating pre-eclampsia.

Average fetal growth depends on the placental vascular function that is operating at its best. Nitric oxide (NO), a calming agent created from the endothelium, plays a significant role in regulating normal fetal placental blood flow because the placenta lacks autonomic innervation. The enzyme NO-synthase (NOS), stimulated by various substances (such as shear stress, serotonin, and bradykinin), produces NO in the endothelial cell. NO diffuses to the vascular smooth muscle cells, stimulating the guanylate cyclase to raise the amount of cyclic guanosine monophosphate (cGMP) inside the cells. The calcium channels then close, the intracellular calcium level drops, and the vessel wall relaxes.[4]

NAC have a role in the oxidative stress pathway, helping in glutathione synthesis and as a free radical scavenger.[5–8] N-acetylcysteine (NAC) transportation across the placenta indicates the potential for maternal NAC supplementation to reach the endothelium of the fetoplacental unit.[9–12] The mechanism of action of NAC involves increasing the intracellular levels of cysteine/glutathione biosynthesis (GSH) and functioning as an oxidant scavenger. The pharmacological effects of this substance encompass the restoration of cellular antioxidant capacity through the replenishment of glutathione levels depleted by free radicals and reactive oxygen species (ROS). Additionally, it inhibits neutrophil activity and the production of tumor necrosis factor (TNF).[13,14] In keeping with this reasoning, we speculate that administering NAC to the fetoplacental vascular bed may enhance endothelial function, particularly that mediated by the NO-pathway, in the placentas of preeclamptic women. This study aims to examine the role of NAC on women with preeclampsia.

MATERIALS AND METHODS

This systematic review aims to find the effectiveness of NAC in managing women with preeclampsia. This study is done according to PRISMA guidelines. Literature search was done using the PubMed and ScienceDirect database.

Search strategy

The keywords used in the search were "N-acetylcysteine" and "preeclampsia". The results following the search were reviewed by the reviewer to determine the eligibility of the study. The inclusion criteria in this study were studies published in English, about the effect of NAC on patients with preeclampsia or in animal model, and published from the year 2000 and forward, while the exclusion criteria were studies not published in English, in vitro, and in patients without preeclampsia.

Selection process

Using the PubMed and ScienceDirect database, 17 and 395 articles were obtained. Reviews were then excluded from both pooled articles, resulting in 12 articles from PubMed and 89 articles from ScienceDirect. Studies examining the effect of NAC in vivo and discussing other substances were excluded. After removing duplicates, a total of 6 articles were screened for eligibility. One study was excluded due to its study population were women without preexisting pre-eclampsia. A total of 5 articles, consisting of 2 human studies[6,15] and 3 animal studies.[16–18] were obtained and included in this systematic review. Article selection process is described in Figure 1.

Risk of bias assessment

Risk of bias assessment in animal studies were done using the SYRCLE's risk of bias tool, this tool examines selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.[19] Cochrane risk of bias tool was used to assess human studies, examining selection bias, performance bias, attrition bias, detection bias, reporting bias, and other bias.[20]

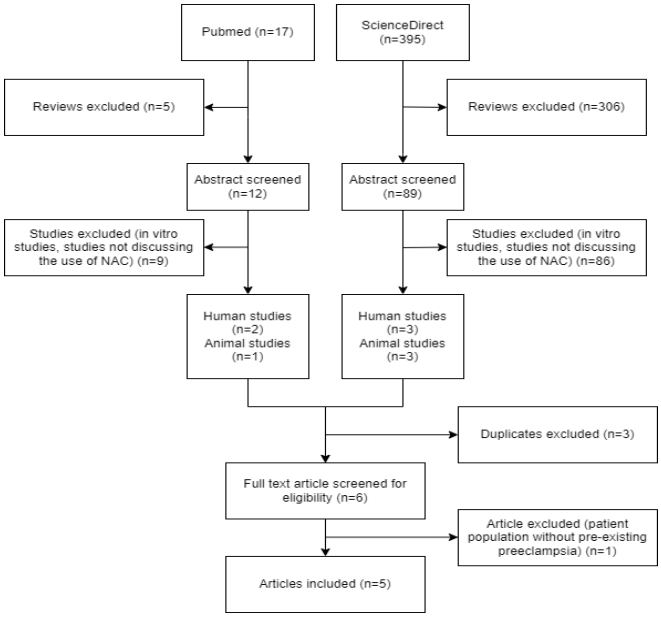

Figure 1. Article selection process

Table 2. Summary of human studies

Author	Year	Country	Dose	Other Interventions	Sample Size		Sample Characteristics	Result
					Intervention	Control		
Motawei, et al.	2016	Egypt	400 mg/day	Methyldopa 250 mg with calcium-channel blockers if hypertension remains uncontrolled, nutritional deficiency correstion therapy, and magnesium	50	50	Patients with pre-eclampsia	Significant increase in intervention group compared to control group in GPx, SOD, ALT, AST, serum creatinine, proteinuria, SBP, and DBP values in both 4 and 6 weeks post intervention. Significant improvement of birth weight and Apgar score (1 and 5 minuters). No significant difference found in MDA value and the rate of maternal complications.
Roes, et al.	2006	Netherlands	3 tablets of 600 mg/ hours until delivery	Antihypertensives, corticosteroids, and magnesium sulfate	19	19	Patients with early onset severe preeclampsia and/or HELLP syndrome between 25 and 33 weeks gestation, excluding those with twin pregnancy, predominantly Caucasian	Significantly less concentration of homocysteine in intervention group compared to control group. No significant difference in plasma thiol levels, treatment-to-delivery interval, gestational age at delivery, maternal complication, neonatal morbidity and morality, birth weight, and Apgar score at 5 minutes.

Table 3. Summary of animal studies

Author	Year	Country	Sample Characteristics	Dose	Result
Ayasolla, et al.	2006	USA	Sprague-Dawley rats with RUPP model	100 mg/kg every 12 hours, first dose given prior to RUPP procedure on day 15/22 of pregnancy	Significant decrease of GSH, GPx, and GR activity accompanied by decreasing Cu/ZnSOD expression in the RUPP group. Increased activity of MnSOD activity in the RUPP model. Changes were observed to be reversed with the administration of NAC.
Chang, et al.	2004	USA	Sprague-Dawley rats with RUPP model	100 mg/kg every 12 hours, first dose given prior to RUPP procedure on day 15/22 of pregnancy	Significant decrease in litter size, pup weight, and pup brain weight in the RUPP group, accompanied with significantly higher MAP. The changes were observed to be attenuated with the administration of NAC.
Chang, et al	2005	USA	Sprague-Dawley rats with RUPP model	100 mg/kg every 12 hours, first dose given prior to RUPP procedure on day 15/22 of pregnancy	Significant decrease in pup weigth and pup brain weight in the RUPP group, accompanied with significantly higher MAP. No significant difference found in litter size. The changes were observed to be significantly improved with the administration of NAC except for pup weight.

Table 4. Risk of bias of animal studies

Authors	Year	Selection Bias			Performance Bias		Detection Bias		Attrition Bias	Reporting Bias	Other
		Sequence Generation	Baseline Characteristics	Allocation Concealment	Random Housing	Blinding	Random Outcome Assessment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
Ayasolla, et al.	2006										
Chang, et al.	2004										
Chang, et al.	2005										

Labels : Low risk; Some concerns; High risk

Table 5. Risk of bias of human studies

Authors	Year	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Incomplete Outcome Data (Attrition Bias)	Blinding of Outcome Assessment (Detection Bias)	Selective Reporting (Reporting Bias)	Other Bias
Motawei, et al.	2016							
Roes, et al.	2006							

Labels : Low Risk; Some Concerns; High Risk

RESULTS AND DISCUSSION

A total of 5 articles were included in this review, consisting of 2 human studies.[15,21] and 3 animal studies.[16,17,22–24]. The inclusion of studies based on animal models were done to supplement more data regarding the effect of NAC in preeclampsia due to there being few human based studies available. The risk of bias in animal-based studies are regarding the blinding of researchers and randomization which are not explicitly stated in the articles. The risk of bias in human based studies are the same in the study done by Motawei, et al, due to there being no explicit statement regarding blinding and randomization.[15]

The results of NAC administration in animal RUPP models, which were done by using a calibrated silver clip placed on the infrarenal aorta and the branches of the right and left ovarian arteries that supply the uterus, were favorable in the administration of NAC. The changes induced by the RUPP procedure were ameliorated by the administration of NAC.[16,17,22] Pup weight, pup brain weight, and MAP were found to be improved using NAC.[16,18] Regarding litter size, one study found there to be a significant difference.[18] and another study didn't find any difference.[16] The resulting measurement of oxidative stress biomarkers indicate a significant improvement in GSH, GPx, GR, and SOD activity in subjects that underwent the RUPP procedure and treated with NAC.[17] This opens the possibility of the potential of NAC to reduce oxidative stress and improve maternal outcomes.

Regarding the human studies, the study done by Motawei, et al. shown a significant improvement in laboratory values (ALT, AST, serum creatinine, proteinuria), improved SBP and DBP measurement, oxidative stress biomarkers (GPx and SOD), and maternal outcomes (birth weight and Apgar score both in 1 and 5 minutes).[15] These findings are conflicting with the study done by Roes, et al., which shown no significant improvement in maternal (birth weight and Apgar score at 5 minutes) and neonatal mortality and morbidity.[21] No significant prolongation of gestational age at delivery were found, indicating the lack of NAC's ability on stabilizing the process of ongoing preeclampsia, which should result in the prolongation of pregnancy. The level of homocysteine, a marker indicating the promotion of formation of ROS, were found to be significantly decreased in the treatment group.[21] The severity and the time of treatment were stated to influence the outcome produced by the study. The dose used in the study could also affect the results, since there is no information regarding the dosing, response time, and optimal duration of NAC administration in preeclampsia.

A study done by Rumiris, et al., shown that the supplementation of antioxidants results in a lower rate of preeclampsia in women with low antioxidant status. This study used plenty of different antioxidants combined, including NAC.[25] Both studies included in this review also didn't find any significant side effects resulting from the use of NAC, even in higher doses, as shown by the study done by Roes, et al. A study done by Chappell, et al and Fu, et al. found a reduction in

preeclampsia rate using antioxidants in women having increased risk of preeclampsia, defined by the study as having an abnormal doppler waveform in either uterine artery at 19-22 weeks' gestation or a history in the preceding pregnancy of preeclampsia necessitating delivery before 37 weeks gestation, eclampsia, or HELLP syndrome. This study, utilizing vitamin C and E, also found a significant reduction on the ratio of plasminogen-activator inhibitor 1 and 2, a marker of endothelial activation and placental dysfunction, suggesting an improvement in endothelial function.[4,26–28]

The limitations of this study are the lack of studies specifically researching the effects of NAC in preeclampsia, leading to our decision to supplement it with animal studies to increase the base of evidence. The dosing of NAC in human studies differ greatly, possibly affecting the benefits derived from NAC supplementation, as there is no prior reference or guidelines discussing the effective dose of NAC supplementation in preeclampsia. The results assessed by the studies also differ in the type of biomarkers measured and clinical outcomes.

Further studies could be done with more specific population regarding time of gestation, severity of preeclampsia, time to treatment, and dosing to further clarify the potential effects of NAC.

CONCLUSION

NAC supplementation in women with preexisting pre-eclampsia had positive effects on oxidative stress biomarkers, laboratory values, and blood pressure. No significant difference was found in the rate of maternal complications.

DISCLOSURES

Conflict of interest

There has no conflict of interest.

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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