N-ACETYLCYSTEINE

RECOMMENDATION

We recommend against the use of intravenous N-acetylcysteine as adjunct treatment for patients with COVID-19 infection. *(Moderate quality of evidence; Strong recommendation)*

Consensus Issues

The panel distinguished between the oral and intravenous (IV) preparations of N-acetylcysteine (NAC), noting in part the cost of the IV agent.

A study included in this review which compared NAC and placebo among suspected or confirmed COVID-19 patients found no significant difference on its primary and secondary outcomes (i.e., mortality, invasive mechanical ventilation and ICU admission). However, NAC may essentially still be used for its other clinical indications (i.e., as mucolytic) on patients with COVID-19, but not necessarily for the treatment of COVID-19.

There were also a few studies included in the review that compared IV-NAC and placebo among ARDS patients, and although it was also noted that NAC has no ancillary role on the treatment of ARDS, it is used for intubated patients for its mucolytic and immunomodulating properties.

EVIDENCE SUMMARY

Should N-acetylcysteine be used as an adjunct treatment for patients diagnosed with COVID-19?

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Key Findings

One randomized controlled trial comparing NAC to placebo with 135 participants was found to have no significant difference compared to control for mortality, invasive mechanical ventilation, ICU admission, length of hospital and ICU stay. A case series of ten respirator-dependent patients who responded to IV NAC showed reduction in inflammatory markers wherein six patients rebounded once NAC was discontinued and eight were discharged while two remained hospitalized. Indirect evidence in a low-quality systematic review of NAC vs placebo in patients with Acute respiratory distress syndrome failed to show any difference in the mortality, but significantly reduced ICU stay.

Introduction

N-acetylcysteine, a well-known mucolytic and antidote against paracetamol intoxication, is a thiol precursor of reduced glutathione with antioxidant properties. Its potential role in COVID-19 treatment has been postulated by several studies to be due to its antioxidant and anti-

inflammatory properties with its conversion to reduced glutathione (GSH). It is found to inhibit reactive oxygen species (ROS) formation and pro-inflammatory cytokines, and increase the number of CD4+ T cells and nitric oxide (NO) production [1,2]. NAC has also been shown to inhibit the NLRP3 inflammasome pathway and gene expression of TNF-α, both linked to inflammatory cell death in SARS-1 patients.[3] Its antibacterial properties, including inhibition of biofilm formation and biofilm disruption, may reduce the risk of secondary bacterial infection as a complication of COVID-19.[4] The protective effect of NAC in reestablishing glutathione levels, scavenging reactive oxygen and supporting mitochondrial bioenergetics may also be of benefit for COVID-19-related liver injury.[5].

Review Methods

Existing randomized controlled trials and living systematic reviews, including COVID-19 databases and CPGs (NICE CENTRAL), publications (PubMed, Google Scholars, Ovid, Herdin), including pre-print (Medrxiv, Biorxiv, Chinaxiv) and trial registries (WHO, ICTRN, ChiCTR, EU) were searched using the following keywords: “N-acetylcysteine”, “acetylcysteine”, “N-acetyl-L-cysteine”, ”NALC”, “NAC” and “adjunct”, RCT, systematic reviews and COVID-19 related terms in the search strategy.

The following PICO criteria were used:

Population	COVID-19 patients, adults 18 years and above, positive for COVID-19, mild-to severe cases, inpatient and outpatient
Intervention	N-acetylcysteine, oral or intravenous form, as single agent used adjunctively with usual care or as per institution/center/hospital standard protocols
Comparator	Placebo with usual care or standard protocols
Outcome/s	Mortality, Clinical deterioration/ development of ARDS, Need for mechanical ventilation, Hospital length of stay, Time to clinical improvement/ recovery, Improvement in Chest CT Scan/ X-ray, Virologic clearance by PCR test, Adverse effects, O2 requirement, Severity of disease, Dosage,
Study Designs	Randomized controlled trials, Systematic Reviews, Cohort studies

Results

There is one randomized controlled trial that compared NAC to placebo in 135 adults with suspected (5%) or confirmed (95%) COVID-19. Patients had a mean age of 58 years, 2/3 of whom had more than 50% findings on computed tomography and required oxygen supplementation. All except one were classified as category 4 or 5 in the WHO 7-point scale. A dose of 21 grams/L of NAC was administered intravenously in two doses over 20 hours for the intervention group (IG) and placebo for control, all patients receiving standard of care which included O_2 supplementation, invasive ventilation and empiric ceftriaxone 2g/day and azithromycin 500 mg/day. They found no significant differences between treated patients and controls in all the primary (need for intubation and invasive mechanical ventilation) and secondary outcomes (time of mechanical ventilation,

length of ICU stay (median = 9, R 5-14, p = 0.557), length of hospital stay(median = 11, R 5.5-19, p = 0.872), and mortality. While NAC is commonly associated with nausea, vomiting and other gastrointestinal symptoms, there was no observable side effect in this study.[8]

There is one case series of ten respirator-dependent COVID-19 patients where IV NAC was administered after one severely affected patient with G6PD-deficient fully recovered. 30 grams NAC given in three doses over 24 hours were given. There was overall reduction in inflammatory markers (C-reactive protein and ferritin) which rebounded in six patients following discontinuation of NAC. Eight of the 10 were eventually discharged. [9]

We found a low-quality systematic review (SR) on NAC among adults with Acute Respiratory Distress Syndrome published in 2019.[7] It included eight RCTs (n=289) and showed no significant difference in mortality (RR 0.83, 95%CI: 0.62 to 1.11, p =0.21, I^2= 0%). However, NAC significantly shortened ICU stay in the random effects model (MD = -4.47 days; 95%CI: -8.79 to -0.14, p=0.04, I^2=46%). There was substantial heterogeneity, small population sizes, and unclear to high risk of bias making the grade of evidence low for this SR.[7]

Recommendations from other groups

The Australian National COVID-19 Clinical Evidence Task Force does not recommend the use of N-acetylcysteine for the treatment of COVID-19 outside of randomized controlled trials with appropriate ethical approval. NAC, however, should still be used for its other established indications in people who have COVID-19.

Clinical practice guidelines from WHO, NICE, Canadian Task Force, UK NHS, EU CDC or PSMID made no recommendations for the use of N-acetylcysteine as an adjunctive treatment of COVID-19.

Ongoing Studies

There are currently 13 registered clinical trials on NAC as an adjunct to treatment, five of which are in combination with other therapeutic drugs and antioxidants. Eight clinical trials with N-acetylcysteine alone, in comparison to other drugs, are listed in Appendix 4.

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Appendix 1: Characteristics of Included Studies

Author, Year	Type of Study	POPULATION	INTERVENTION	COMPARATOR	OUTCOMES
De Alencar, 2020 Sept	RCT	135 severe COVID-19 patients (confirmed or suspected) with O2 sat <94% or RR>24/min	21 gm IV NAC for 20 hours (14 gm in first 4 hours then 7 gm in next 16 hours)	Dextrose 5%	Primary endpoint: need for mechanical ventilation 2ndary endpt: time of mechanical ventilation, admission to ICU, time in ICU, mortality
Ibrahim, 2020	Case series	One severe case of COVID-19 with G6PD deficiency and 9 respirator-dependent COVID-19 pxs	2 received bolus doses of 30gm and 20gm each; 8 received 600 mg q12h for 1 week; 8 requiring VV ECMO	none	Outcome noted: hospital discharge; reduction in serum CRP and ferritin levels;
Lu, 2019	Meta-analysis	8 studies included with N = 289 ICU patients; 6 reported mortality; 5 reported PaO_2/FiO_2; ; 3 reported length of ICU stay; population of ARDS patients	iv NAC (n =148) dose range 40-190 mg/kg	Placebo (5% dextrose or isotonic saline solution) (n= 141)	Primary outcome: overall mortality; Secondary outcomes: length of ICU stay, duration of mechanical ventilation, glutathione levels, PaO_2/FiO_2

Appendix 2: GRADE Evidence Profile

Question: NAC compared to placebo for Covid-19

Setting: adults with mild to severe Covid-19

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NAC	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 5 days to 19 days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	9/68 (13.2%)	9/67 (13.4%)	**RR 1.01** (0.43 to 2.40)	**1 more per 1,000** (from 77 fewer to 188 more)	⨁⨁⨁◯ MODERATE	
Invasive mechanical ventilation (follow up: range 4 days to 15 days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	14/68 (20.6%)	16/67 (23.9%)	**RR 1.16** (0.62 to 2.18)	**38 more per 1,000** (from 91 fewer to 282 more)	⨁⨁⨁◯ MODERATE	
ICU admission (follow up: range 4 days to 15 days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	32/68 (47.1%)	29/67 (43.3%)	**RR 0.92** (0.63 to 1.33)	**35 fewer per 1,000** (from 160 fewer to 143 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Confidence intervals are wide and traverses 1 in all outcomes, and therefore does not differ significantly from placebo.

Question: NAC compared to placebo for Acute REspiratory Distress Syndrome

Setting: Adults years and above with moderate to severe ARDS

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NAC	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
6	randomised trials	serious [a]	serious [b]	not serious	not serious	none	55/123 (44.7%)	46/127 (36.2%)	**RR 0.82** (0.57 to 1.11)	**65 fewer per 1,000** (from 156 fewer to 40 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Only one study had low risk of bias. the rest were either unclear or had high risk with respect to randomization, allocation concealment)

b. The studies had differences in their diagnostic criteria for ARDS, the formulation of NAD administration and mortality endpoints.

Appendix 3: Forest Plots

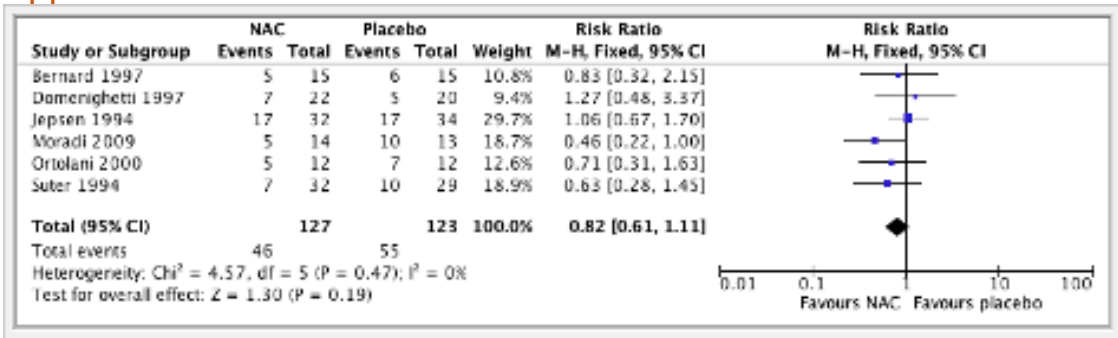

Figure 1. NAC vs Placebo in ARDS. Forest plot of 6 studies which measured mortality.

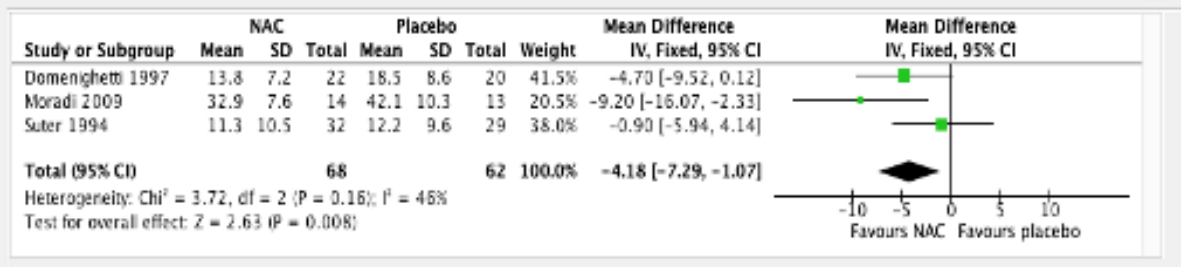

Figure 2. NAC vs placebo in ARDS. Forest plot on the duration of stay in the ICU in mean number of days (3 RCTs)

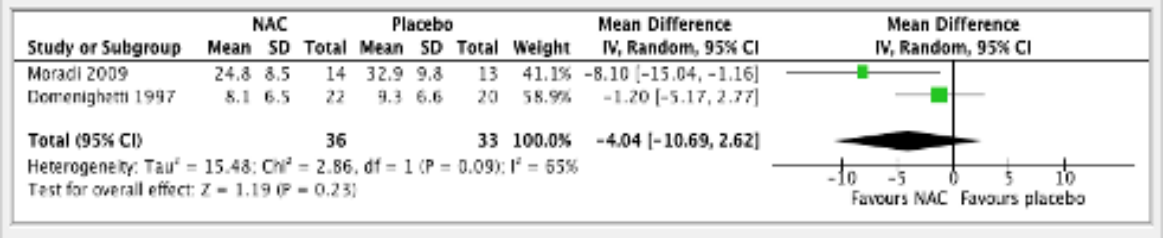

Figure 3. NAC vs placebo in ARDS. Forest plot on the duration of mechanical ventilation in mean number of days. (2 RCTs)

Appendix 4: Characteristics of Ongoing Studies

NO.	TITLE	POPULATION	INTERVENTIONS	COMPARATOR	OUTCOME MEASURES
1	Treatment of 2019-nCoV pneumonia with NAC; UTN U1111-1250-3564	adult >18 years admitted with ARDS 2 Covid; 140 px to be recruited	IV NAC 300mg/kg total dose; 1st dose 200mg/kg then 100 mg/kg in 16 hours	Placebo IV	ABGs, reduction in in-hospital MR; reduction in need for endotracheal intubation
2	Evaluation of the efficacy and safety of oral N-acetylcysteine in treatment and recovery of patients with COVID-19 who are under treatment with routine protocols; IRCT 20200623047897N1	adults admitted with C19 moderate to severe but stable	Regimen 1 OR Regimen 2 + 600 mg oral NAC TID	Regimen 1: Kaletra + HCQ and Regimen 2: Atazanavir + Ritonavir + HCQ	fever/cough/dyspnea/o2 level/duration of; time to improv; secondary = O2 sat, rehospitalization, duration of hospitalization symptoms, i.e. cough shortness of lethargy; administration/laboratory parameters/ radiologic changes/ICU admission/death
3	A Study of N-acetylcysteine in Patients With COVID-19 Infection; NCT04374461	adults 18 years and older mod-severe; 84 patients to be recruited	NAC	peripheral blood	Outcome Measures: Arm A: no. of patient successfully extubated and/or transferred out of critical care due to clinical improvement; Arm B: no. of patients who are discharged from the hospital due to clinical improvement
4	Trial of Famotidine & N-Acetyl Cysteine for Outpatients With COVID-19; NCT04545008	Adult 18 years and older diagnosed with covid-19 (severity not mentioned); 42 participants	Arm 1: Oral NAC 600 mg TID; Arm 2 Oral NAC 1200 mg TID; Arm 3 Oral NAC 1800 mg TID	Combinations of NAC 600 mg, 1200mg, 1800 mg TID with Famotidine 20mg, 40 mg, 80 mg TID	Resolution of Covid; No. of participants with treatment-related adverse events as assessed by CTCAE v5.0; rate of hospitalization;
5	Inflammatory Regulation Effect of NAC on COVID-19 Treatment; NCT04455243	Adult 18 years and older admitted to hospital, on oxygen supplement; 1180 participants	NAC 150 mg/kg q12hrs x 14 days (oral/IV)	Placebo	Time to recovery
6	Efficacy of N-Acetylcysteine (NAC) in Preventing COVID-19 From Progressing to Severe Disease; NCT04419025	Adult 18 years and older, healthy, known or suspect with mild to mod Covid-19 disease; 200 participants	Inpatients: NAC 25mg/kg PO q4hrs until discharge; NAC 1200 PO BID x 1 week post-discharge; OPD NAC 2400 mg PO then 1200 mg PO BID x 2 weeks	No NAC	Decrease in respiratory rate; hospital length of stay (LOS); need for mechanical ventilation; length of time intubated; need for hospitalization; recovery disposition
7	A Study to Evaluate OP-101 (Dendrimer N-acetyl-cysteine) in Severe Coronavirus Disease 2019 (COVID-19) Patients; NCT04458298	Adult 18 years and older with severe Covid-19; 24 participants	OP-101 (dendrimer NAC) on single IV infusion of 1) OP-101 2 mg/kg; 2) 4 mg/kg; and 3) 8mg/kg	Placebo	No. of participants with Adverse events (assessed by CTCAE v4.0); time to improvement in clinical status assessment (WHO 7-pt ordinal scale); time to resolution of fever (>48 hours) without antipyretics for patients with fever; time to improved O2'n; Change in WHO 7-pt ordinal scale; time to discharge from hospital; %age of alive patients; No. of days with Resting

NO.	TITLE	POPULATION	INTERVENTIONS	COMPARATOR	OUTCOME MEASURES
					RR > 24/min, hypoxemia,
8	Antioxidants as Adjuvant Therapy to Standard Therapy in Patients With COVID-19; NCT04570254	Child, adult, older adult; 11 participants	1) Vitamin C 1 gm q12hr; 2) Vitamin E 800 mg q24 hours; 3) Melatonin 50 mg q24h; 4) NAC 600 mg q12h (all for 5 days)	Pentoxifylline 400 mg q12hrs administered to all patients	Death from any cause; percentage required orotracheal intubation, assisted mechanical ventilation, stay in ICU, measure lipoperoxidation in base and post-therapy samples, total antioxidant capacity, oxidative and antioxidant stress; effect of antioxidant therapy at level of organ failure