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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

ORIGINAL ARTICLE

What is the optimum thiamine dose to treat or prevent Wernicke's encephalopathy or Wernicke–Korsakoff syndrome? Results of a randomized controlled trial

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Abstract

Background: The primary cause of Wernicke–Korsakoff syndrome (WKS) is thiamine deficiency, and more than 90% of cases are reported in alcohol-dependent patients. While observational studies show parenteral thiamine administration drastically reduced WKS-related mortality, relevant treatment trials have never been conducted to determine the optimum thiamine dose.

Methods: Two double-blind, parallel groups, randomized controlled trials (RCTs) were conducted to determine the optimal thiamine dose required for (1) the prevention of Wernicke's encephalopathy (WE), the acute phase of WKS, in asymptomatic but "at-risk" alcohol misuse patients (Study 1) and (2) the treatment of WE in symptomatic alcohol misuse patients (Study 2). Each study had a dosage regimen comprising three parenteral thiamine doses that were allocated at a ratio of 1:1:1. Study 1: Asymptomatic At-Risk patients ($N = 393$) received either 100 mg daily, 100 mg thrice daily, or 300 mg thrice daily, for 3 days. Study 2: Symptomatic patients ($N = 127$) received either 100 mg thrice daily, 300 mg thrice daily, or 500 mg thrice daily, for 5 days. Cognitive function was the primary outcome, assessed using the Rowland Universal Dementia Assessment Scale, two Cogstate subtests, and an adapted Story Memory Recall test. Secondary analyses examined differences in neurological function (ataxia, oculomotor abnormalities, and confusion) at follow-up.

Results: No significant differences were observed between any of the dosage conditions for either Study 1 or Study 2 on cognition or neurological functioning. This real-world study found that having a clinically unwell target population with high comorbidity and multiple presentations, coupled with challenges in cross-cultural assessment is likely to complicate RCT findings.

Conclusions: The results of this study showed no clear benefit of high dose thiamine over intermediate or lower doses of thiamine, over the time intervals examined, for the treatment and prevention of cognitive and neurological abnormalities related to WKS.

Trial Registration: ACTRN12614000327684; 26/3/2014.

Several study limitations temper the interpretation of these findings. Nevertheless, the absence of conclusive evidence for the superiority of high-dose thiamine supports a recommendation for patient-specific treatment, while ensuring that the potential impact of other biochemical factors (e.g., magnesium and other B vitamin deficiencies) are considered and corrected if necessary.

KEYWORDS
dose, thiamine, treatment trial, Wernicke–Korsakoff syndrome

INTRODUCTION

The primary etiology of Wernicke–Korsakoff syndrome (WKS) is thiamine deficiency, and more than 90% of cases of WKS are reported in alcohol-dependent patients (Thomson & Marshall, 2006a). Many alcohol-dependent people suffer severe, prolonged nutritional deficiencies and alcohol acts to impair the absorption and utilization of thiamine in the brain (Hoyumpa, 1983; Pitel et al., 2011; Scalzo et al., 2014; Thomson & Marshall, 2006b). Dietary thiamine provides an essential coenzyme for diverse metabolic activities, perhaps most importantly for the energy (ATP) cycle in cells. Deficiency may lead to reduced metabolic activity or cell death (Chiossi et al., 2006; Donnino et al., 2007; Thomson et al., 2012). Both neurons and astrocytes (Hazell & Butterworth, 2009) are particularly susceptible to thiamine deficiency, and deficiency may lead to a spectrum of neurological and other impairments, only the most severe of which are clinically obvious.

Wernicke–Korsakoff syndrome consists of an acute, reversible component called Wernicke's encephalopathy (WE), and a chronic component known as Korsakoff's syndrome (KS) that is reversible in some patients (Scalzo et al., 2014, 2015; Victor et al., 1989), as originally described by Korsakoff (Victor & Yakovlev, 1955). Despite its high prevalence in some settings, a rapid, sensitive laboratory test is not available, and the wide spectrum of clinical symptoms makes diagnosis difficult. Therefore, WKS is under-diagnosed (Galvin et al., 2010; Isenberg-Grzeda et al., 2012; Sechi & Serra, 2007). The postmortem prevalence of WKS is estimated at 1%–2%, and the clinical prevalence of WKS neuropathology is estimated to be 5 to 100 times more common than that indicated by the conventional clinical diagnosis of acute WE based on the "classic" triad of eye signs, ataxia, and mental impairment, or of KS based on chronic amnesia (Bowden, 1990; Scalzo et al., 2015; Thomson et al., 2002; Torvik, 1991). Consequently, diagnostic criteria for WKS were revised to make a presumptive diagnosis in malnourished or alcohol-dependent persons showing any signs of cognitive or neurological compromise (Caine et al., 1997; Reuler et al., 1985; Victor, 1994). Where the epidemiology has been well-studied, there is strong evidence of an increasing frequency of WKS that is primarily associated with socioeconomic factors (Thomson & Marshall, 2006a). The prevalence and consequences of WKS in Australia are thought to be high among Indigenous Australians (Department of Health & Aging, 2007) due to a myriad of health and socioeconomic risk factors.

It had been thought for a long time that the classic triad had high diagnostic sensitivity for WE, effectively identifying those in need of treatment, however, it was later suggested that up to 90% of cases did not display the classic triad (Day et al., 2008; Harper et al., 1986; Victor, 1994). Diagnostic criteria have been revised from the classic triad to also include dietary deficiencies and require only two of the four signs (Caine et al., 1997). The need for evidence-based treatment guidelines is highlighted when it is recognized that milder, subclinical WKS may be preventable with adequate thiamine treatment. This variant of WKS is often missed or misdiagnosed as nonspecific alcohol-related dementia, a category that is thought to account for 9%–22% of all clinical dementias (Gupta & Warner, 2008; Kopelman et al., 2009; Ridley et al., 2013; Ritchie & Villebrun, 2008). One large neuropathological survey showed that alcohol-related dementia was the most common diagnosis antemortem in patients found to have chronic WKS at postmortem, highlighting inadequacies in clinical assessment for WKS and difficulties in diagnosis of cases often relatively asymptomatic (Torvik, 1991; Victor, 1994). The risk of failure to diagnose and treat subclinical WKS is that the disease may advance to more severe and chronic WKS. Therefore, a successful thiamine treatment trial and development of an evidence-based protocol for the treatment of milder, subclinical WKS, before it develops into a disabling and potentially irreversible form of WKS, may provide direct benefits for reducing the growing healthcare burden associated with dementia (Alzheimer's Australia, 2009; Radford et al., 2019).

Common though WKS is, there is a paucity of knowledge regarding the optimal thiamine dosage for the treatment of WKS including the acute WE phase (Day et al., 2008). A Cochrane review to determine the efficacy, dose, and duration of thiamine treatment for patients with WKS as a consequence of excess alcohol found very few treatment trials have been conducted to determine thiamine dosing regimes (Day et al., 2008, 2013). One of the reasons for inattention to quality randomized controlled trial (RCT) evidence for treatment of acute WE lies in the all-or-none effect observed in early observational studies. Mortality was drastically reduced with acute administration of thiamine (Day et al., 2008; Victor, 1994). The abovementioned, Cochrane review reported only one randomized treatment trial (with sufficient data) assessing the effect of different doses (up to 200 mg), which was from our group. This study randomized 107 detoxifying patients to five alternative daily treatments (5, 20, 50, 100, or 200 mg) and concluded that 200 mg was superior to the mean of all other doses (Ambrose et al., 2001). Based largely on this trial, uncontrolled case studies and empirical clinical practice, clinical guidelines from the European Federation of Neurological Societies recommend 200 mg IV thrice daily, although acknowledging

that while this dose has been effective for nonalcohol-related WKS, higher doses may be required for alcohol-related WKS (Galvin et al., 2010). The Royal College of Physicians also produced guidelines recommending 250 mg IV once daily when used prophylactically and 500 mg three times daily for presumptive diagnosis of WKS including acute WE, both for between 3 and 5 days (Thomson et al., 2002). Oral thiamine supplementation is inadequate as no more than 4.5 mg is absorbed from oral doses exceeding 30 mg (Thomson, 2000). In Australia, like the rest of the world, there is no established consensus for thiamine dosing regimens, with many hospitals implementing their own protocols (Pruckner et al., 2019). While original recommendations and product information sheets suggest dosing regimens of 100 mg IV daily, this recommendation has not been clinically validated and has been criticized as inadequate (Donnino et al., 2007; Nakamura et al., 2018).

The aim was to conduct two studies (with differing treatment durations) to evaluate the effectiveness of two dosage regimens, each comprising three different parenteral (i.e., intravenous) thiamine doses: Study 1: for remediating or preventing subclinical WE in asymptomatic at-risk alcohol using patients and Study 2: for treating WE among symptomatic alcohol using patients. It was hypothesized that higher doses (viz., Study 1: 300 mg thrice daily for 3 days and Study 2: 500 mg thrice daily for 5 days) of intravenous thiamine would lead to greater improvements in specific WE cognitive and neurological dysfunctions compared to the lower doses (viz., Study 1: 100 mg daily or 100 mg thrice daily both for 3 days and Study 2: 100 mg thrice daily, or 300 mg thrice daily both for 5 days). The dose ranges were intended to encompass the range of doses in current practice, which, in the absence of evidence-based guidelines, varies widely (Alim et al., 2017; Nakamura et al., 2018; Pruckner et al., 2019).

MATERIALS AND METHODS

Trial design

The two studies were randomized, double-blind, three-arm, parallel groups trials (allocation ratio 1:1:1) conducted at one site in the Northern Territory (NT) of Australia to determine the optimal parenteral thiamine dose for Study 1: the prevention of WE or WKS in asymptomatic "at-risk" patients and Study 2: the treatment of WE (acute WKS) in symptomatic patients. Patients were separated by symptom group (i.e., asymptomatic at-risk or symptomatic) and then randomized at the individual level upon commencement of their inpatient medical admission. While the study allowed for re-enrolment of participants on subsequent medical admissions (if greater than 1 month since the last parenteral thiamine was administered), only the first complete set of data from each participant was included in the analysis. For example, participants meeting inclusion criteria were entered into the study at the time of admission, regardless of whether or not they had entered the study before, as it was considered a separate episode of WE (with the noted medical review that the patient at previous discharge demonstrated no WKS symptoms or signs at discharge). If the data were complete from the first admission to the study, this data were included in the analysis and additional episodes were excluded. If the data from the first admission were incomplete (e.g., no follow-up cognitive data) this admission was excluded and data from the next admission that was complete (i.e., had both a baseline and follow-up cognitive score) was included such that each participant was only included once and between-subject data remained independent.

Participants and setting

The study setting was a small outer-regional, general hospital in Alice Springs in the NT of Australia. Approximately 30% of the NT population identify as Aboriginal or Torres Strait Islander (hereafter respectfully termed "Indigenous") and Indigenous people represent approximately 70% of consumers in the NT public hospital services (NT Government Department of Health, 2016). The Central Australian region of the NT has over 17 different Aboriginal language groups. The study setting therefore required accommodation of multiple cultural, language, and health literacy differences.

Eligible participants were Indigenous and non-Indigenous adults aged between 18 and 65 presenting to the Alice Springs Hospital (ASH) with a history of heavy alcohol use within the last 3 months defined by AUDIT-C scores above 4 or consumption of greater than 60 g beverage alcohol (i.e., 6 Australian standard drinks[1]) per day or 80 g (i.e., 8 Australian standard drinks) per binge. The legal drinking age in Australia commences at 18 years, and this age also defines adulthood, hence the age range for the study of 18 to 65 years. Exclusion criteria were pregnancy, acute neurological, or cognitive impairment clearly unrelated to presumed thiamine deficiency or WKS, intubation, vasopressor therapy for hypotension, dialysis treatment, acute exacerbation of a psychiatric illness, treatment with parenteral thiamine in the past 4 weeks, or received a statim thiamine dose >300 mg prior to enrolment (asymptomatic at-risk patients only). Participants were classified as "Asymptomatic, At-Risk" of WE if they had a history of heavy alcohol use in the past 3 months and were identified as at nutritional risk but displayed no neurological symptoms. Nutritional risk was considered present where the patient met two of the following criteria: BMI <18 or >30, comorbid chronic illness (e.g., hepatic, respiratory, renal, thyroid disease, and diabetes) that is poorly controlled or biochemical markers indicated nutritional deficiency (magnesium <0.7 mmol/L, albumin <37 g/L, hemoglobin <115 g/L, or red cell mean corpuscular volume <78 or >100 fl). Participants were classified as "Symptomatic" of WE if they had a history of "heavy" alcohol use (as defined above) and displayed two or more clinical signs of oculomotor abnormalities, ataxia, confusion, or nutritional risk (as defined above). Participant flow through the studies is presented in Figures 1 (Asymptomatic At-Risk) and 2 (Symptomatic).

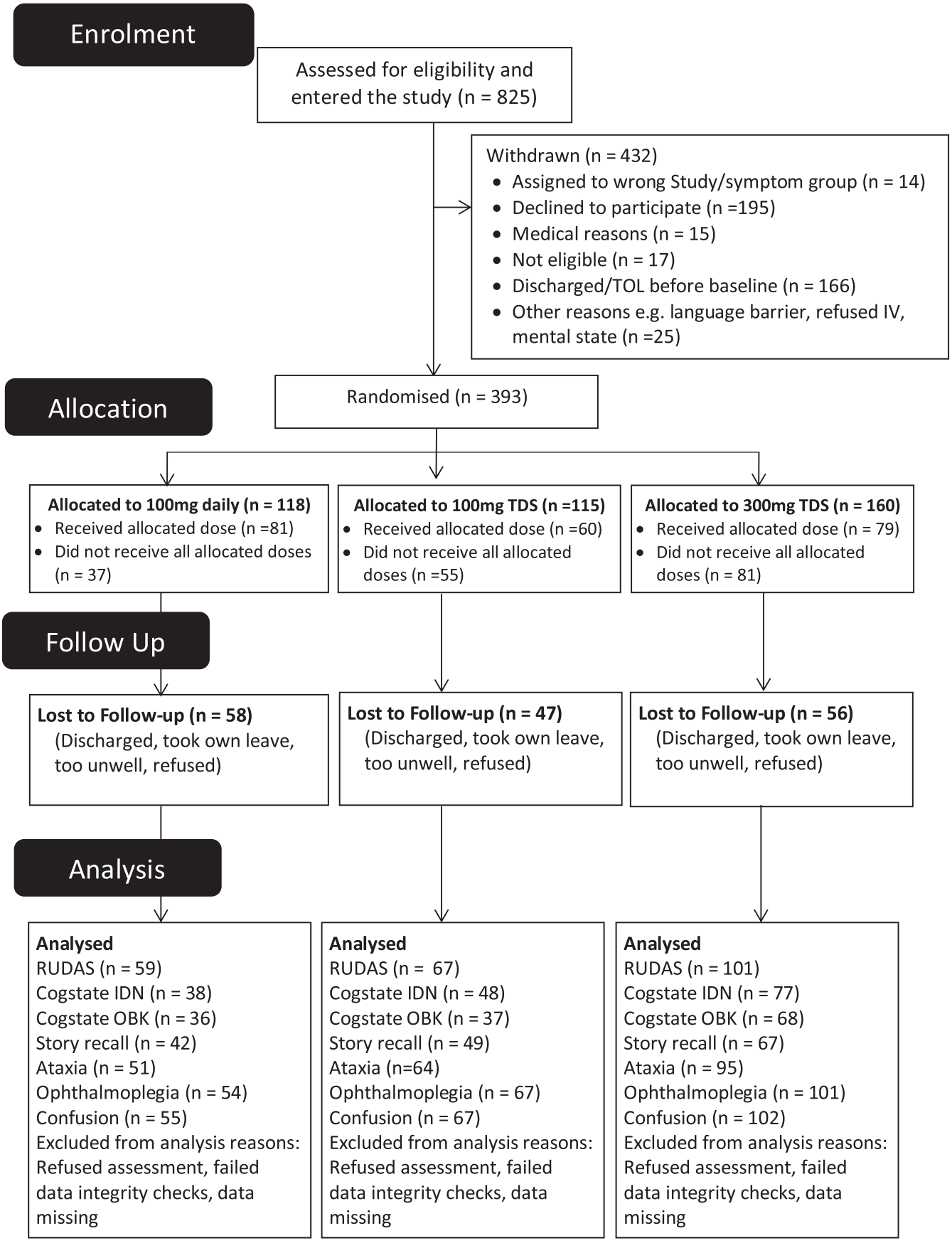

FIGURE 1 CONSORT flow diagram for asymptomatic at-risk participants

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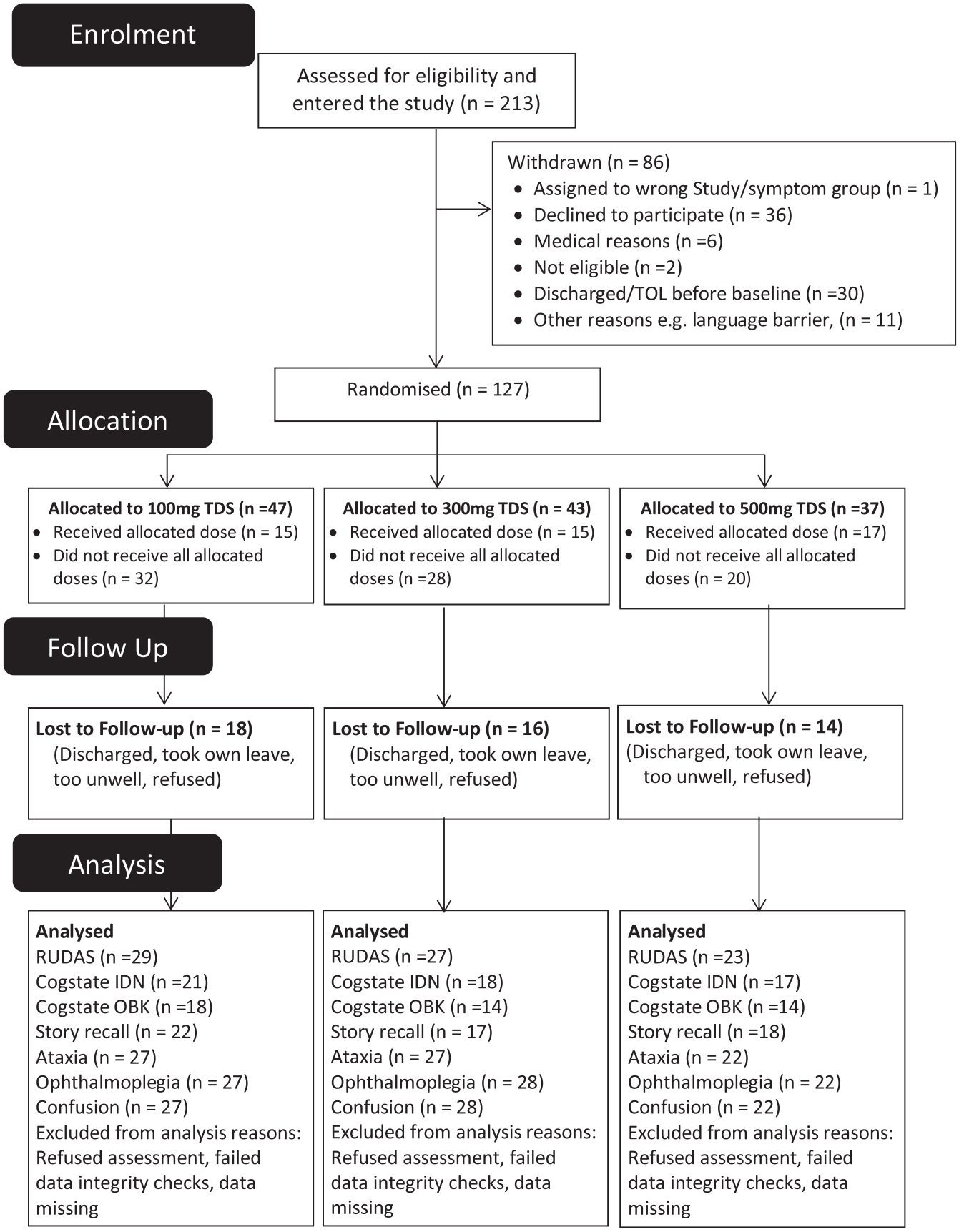

FIGURE 2 CONSORT flow diagram for symptomatic participants

Interventions

The primary objective for the Study 1 Asymptomatic At-Risk group was to evaluate any differences in clinical and neuropsychological outcomes under three treatment conditions of intravenously administered thiamine:

(i) 100 mg per day for 3 days (i.e., ASH usual treatment for asymptomatic alcohol-dependent patients).
(ii) 100 mg thrice daily for 3 days (i.e., ASH usual treatment for at-risk patients).
(iii) 300 mg thrice daily for 3 days (i.e., ASH high-dose usual treatment for symptomatic patients).

The primary objective for the Study 2: Symptomatic of WE group was to evaluate any differences in clinical and neuropsychological outcomes under three treatment conditions of intravenously administered thiamine:

(i) 100 mg thrice daily for 5 days (i.e., a common Australian usual treatment for symptomatic patients).
(ii) 300 mg thrice daily for 5 days (i.e., ASH usual treatment for symptomatic patients).
(iii) 500 mg thrice daily for 5 days (UK College of Physicians recommended dose for symptomatic patients) (Thomson et al., 2002).

The Alice Springs Hospital protocol is to administer 100 mg thiamine hydrochloride intravenously in a 100 ml bag of normal saline (0.9%) infused over 30 min to patients presenting to the emergency department with an alcohol use history. Therefore, a statim (i.e., single, once-only) dose of 100 mg IV thiamine administered prior to enrolment was treated as the first study dose. While this was protocol, this statim dose was not consistently delivered by hospital staff prior to participant enrolment in the study due to factors including inclination of treating physician, initial detection of alcohol misuse, or dose delayed due to department workload. Participants could be enrolled up to 24 h following the initial statim dose. For those randomized to 300 or 500 mg, a top-up dose was given immediately following randomization to those who had received the initial statim dose. In each study (Asymptomatic At-Risk or Symptomatic), participants were randomly assigned at a ratio of 1:1:1 to receive one of the three parenteral thiamine dose conditions for that study. Thiamine administration occurred as described above. There was no placebo condition as it would be unethical to withhold treatment to participants considered either at-risk or symptomatic of WE where it is well acknowledged that untreated deficiency carries a significant risk of morbidity and potential mortality (Ambrose et al., 2001; Day et al., 2013). The aim was to determine the optimal dose, not to determine whether thiamine is effective.

Outcomes

Data for Study 1 and Study 2 were analyzed separately. The primary outcome was the difference in cognitive performance at follow-up (3 or 5 days, respectively) as measured by the Rowland Universal Dementia Scale (RUDAS), CogState choice reaction time, Cogstate one back (OBK), and story recall total score. Secondary outcomes included identified neurological abnormalities.

Due to differences in language and cultural beliefs, reliable cognitive assessment for Indigenous Australians is difficult as mainstream tests typically rely on unfamiliar concepts, content, and values. The assessment battery used was therefore carefully selected for brevity and pilot tested for test appropriateness for the target group, given the large proportion of Indigenous Australians accessing hospital care in this study setting (Dingwall et al., 2017).

Standardized cognitive assessments

Rowland Universal Dementia Assessment Scale

The RUDAS is a widely used cognitive screening test that provides an overall cognitive score based on measures of memory, body orientation, praxis, drawing, judgment, recall, and language (Storey et al., 2004). It is a short cognitive screening instrument designed to minimize the effects of cultural familiarity and language diversity on the assessment of baseline cognitive performance. The RUDAS is used extensively by staff at ASH and was considered the best available and well-accepted cognitive mental status test for alcohol-related conditions in this clinical setting.

CogState

CogState is a computerized cognitive assessment and has been evaluated for use in research with both Aboriginal and non-Aboriginal populations (Dingwall et al., 2009, 2010, 2012; Dingwall, Maruff, & Cairney, 2011; Dingwall, Maruff, Fredrickson, et al., 2011). The Identification and One Back subtests were used to measure choice reaction time (Choice RT) and working memory, respectively. For each of these tests, a playing card is presented on the computer screen and the participant is asked to respond as quickly as possible with "yes" or "no" using keys on the keyboard according to a specified rule (i.e., "is the card red?" and "is the previous card the same?").

Story Recall Memory Test

A Story Recall Memory Test (SRMT) is a verbal memory assessment tool like the logical memory subtest of the Wechsler Memory Scale-IV (Wechsler et al., 2009). Logical memory has been found to be a reliable measure for evaluating verbal memory function. Individuals are read a short prose passage and asked to recall as many details as possible. The SRMT consists of two stories that were adapted for cultural relevance to Central Australia.

The stories were administered either in English or an Aboriginal language spoken by the research participant (via audio recording, choice of five languages available) according to participant preference. The participant listened to the first story and was asked to recall the story immediately afterward. The second story was then delivered, and the patient was again asked to recall the story immediately afterward.

Standardized neurological examination

The baseline standardized neurological examination was the routine ASH addiction medicine neurological examination and was conducted by a trained research nurse or project officer, blinded to treatment condition. This examination was used to identify and quantify abnormalities of orientation and mental function, ocular motility including gaze palsies, cranial nerves III, IV, and VI, nystagmus, balance, posture, coordination, gait, and peripheral sensation. Nystagmus had to be sustained (i.e., reproducible) to be considered abnormal and meet oculomotor abnormality criteria for the study.

Sample size

The target enrolment was 225 participants for each of Study 1 and 2 (total 450), comprising 75 participants in each treatment condition in each study. The sample size calculation aimed to detect a minimum difference of 2.1 points on the RUDAS (about one-half of one standard deviation or a Cohen's *d* of 0.5) with 90% power and an alpha of 0.05 (Cohen, 1988; Wolf & Cornell, 1986). The sample size was calculated using Stata version 15.1 for analysis of covarince (ANCOVA) and dictated that to detect the above difference with 90% power, an alpha of 0.05 and three treatment conditions, and a sample size of 64 per treatment condition was required (assuming baseline data are correlated $r = 0.7$ to the final day of treatment data). Allowing for approximately 15% attrition, the study aimed to recruit 75 participants for each treatment condition.

Randomization

The Menzies biostatistics group (independent staff statistician) drew up the randomization schedule using a computerized random number generator, with restricted randomization (blocks of varying sizes) to conceal allocation and ensure that approximately equal numbers of participants were allocated to each treatment condition. Separate randomization schedules were created for each Study (i.e., Asymptomatic At-Risk and Symptomatic) and investigators, research officers, and participants were blind to these dosing schedules. The study doses were administered according to the randomization code using opaque sealed envelopes (for each study separately).

This was a pragmatic RCT aiming to resemble usual care (Dal-Ré et al., 2018). The Central Australian Human Research Ethics Committee (HREC) and the HREC for the NT Department of Health and Menzies School of Health Research approved delayed oral consenting of participants as participants were potentially cognitively impaired, all received the study drug, it resembled usual care, and timely clinical treatment was paramount (HREC# 14-2183 and HREC# 14-226). Thus, participants were randomized prior to obtaining consent. Following screening, the addiction medicine team selected the next envelope in the sequence based on the participant's symptom group. Participants were allocated to each dose condition at a ratio of 1:1:1. The treatment allocation was concealed from participants.

Blinding

As described above, study investigators, participants, and outcome assessors were blinded to treatment dose. All participants received thiamine, however, they were not told which dose they were receiving. Where a few inadvertent violations of blinding occurred among research officers providing outcome assessment, these cases were noted and another research officer who was blind to treatment dose conducted the outcome assessment instead.

Statistical methods

All participants randomized who completed all study visits and for whom complete data were available were included in the analyses.

Descriptive statistics for baseline characteristics are provided by the study and randomization group. Continuous variables are summarized with mean and standard deviation (SD) when appropriate, or median and interquartile range when not normally distributed, and categorical variables are summarized with frequency and percentage.

Data for each study were analyzed separately using the same analysis plan as set out below. Continuous outcome measures on the final day of treatment were compared between the treatment conditions, and adjusted for the outcome measure at baseline level using an ANCOVA approach, with transformations applied to the outcome measure where necessary. The primarily planned comparisons for each study were to contrast each adjacent condition. Binary neurological data were analyzed using logistic regression adjusting for the outcome measure at baseline.

All analyses were conducted as completers or per-protocol analyses, that is, those with complete outcome data were analyzed according to their allocated condition, regardless of whether they received all doses. For the reasons explained below, an intention-to-treat analysis was not undertaken.

RESULTS

Participants

For the Asymptomatic At-Risk group, 118 participants were allocated to 100 mg daily, 115 to 100 mg TDS, and 160 to 300 mg TDS (see consort diagram in Figure 1). For the Symptomatic group, 47 participants were allocated to 100 mg TDS, 43 to 300 mg TDS, and 37 to 500 mg TDS (see consort diagram in Figure 1). Although we aimed for an allocation ratio of 1:1:1, randomizing early, prior to consenting, and removal from study to prioritize clinical care, led to some unequal allocation between dosage conditions. Baseline descriptive statistics for each group are presented in Table 1. Follow-up was achieved for 58% of the sample for the Asymptomatic At-Risk group and 62% for the Symptomatic group. The following percentages relate to those followed-up and included in the analyses. For Study 1 (Asymptomatic At-Risk), 93% of those allocated to 100 mg daily, 70% allocated to 100 mg TDS, and 65% of those allocated to 300 mg TDS received all doses as per protocol. For Study 2 (Symptomatic), 50% of those allocated to 100 mg TDS, 39% allocated to 300 mg TDS, and 70% of those allocated to 500 mg TDS received all doses as per protocol.

Data collection occurred from September 2014 to March 2019. The trial was extended for 2 years to try to achieve the required sample size. For Study 1: Asymptomatic At-Risk patients, the trial ended when complete datasets were achieved for the proposed sample size. For Study 2: Symptomatic patients, the trial ended prior to reaching the required sample size due to a significantly reduced rate of recruitment (i.e., <1 participant per month) and impending funding expiry.

Cognition

There were no significant differences between the three dosage conditions for any of the cognitive outcome measures across either Study (see Table 2 and Figure 3). There was a marginally significant difference in story memory recall between the 300 mg TDS and the 100 mg TDS conditions for the Asymptomatic At-risk group only. See Table 2 for follow-up means (SDs) and ANCOVA results.

Neurological symptoms

Ataxia was considered present if one or more of the following were present: abnormal gait, upper or lower limb dysmetria, or abnormal Romberg's test. Oculomotor abnormalities were considered present if one or more of the three eye signs of nystagmus, abnormal range of movement, or diplopia were present. Confusion was considered present if participants responded abnormally to either the orientation or confusion questions in the standard examination. Logistic regression was performed to ascertain the effect of treatment dose on the likelihood that participants would have each of the neurological symptoms ataxia, oculomotor abnormality, or confusion at follow-up, while controlling for baseline symptoms. The logistic regression models were all statistically significant for each ataxia, oculomotor abnormality, and confusion for each of Study 1 and Study 2, however, only baseline symptoms significantly explained any of the variances in the model. There was no significant impact of treatment dose on any neurological symptom for either study. See Table 3 for the results of the logistic regression. Alternate assessment of neurological signs taken by the addiction medicine staff prior to randomization elicited fewer abnormal signs (Table 1). When these variables were included in analyses instead of the study baseline neurological assessment, they produced fewer significant results (i.e., baseline neurological abnormalities did not predict signs at follow-up).

Posthoc analyses

To ensure that any important effects excluded from the planned analysis were not overlooked, a series of posthoc analysis of variance were conducted on the outcome variables above. To minimize the risk of Type I errors a "total abnormal neurological signs" variable was created, which was treated as quasi-continuous. The analysis included the demographic and baseline variables listed in Table 1, blood alcohol level on admission, baseline benzodiazepine level, treatment regimen compliance, total thiamine medication consumed in the last 12 months, and route of previous thiamine administration (oral or parenteral). Covariates were dummy coded as appropriate.

In these analyses, age had a significant positive effect on total neurological signs in both the Asymptomatic At-Risk group (partial eta-squared 0.11) and Symptomatic group (partial eta-squared 0.18). AUDIT-C scores had a significant negative effect on the RUDAS score at the outcome (partial eta-squared 0.04) in the Asymptomatic At-Risk group. In the Symptomatic group, total thiamine consumed in the last 12 months was negatively associated with total neurological signs (partial eta-squared 0.108) and baseline magnesium levels were positively related to Story recall (partial eta-squared 0.10).

In a separate set of posthoc analyses, statim dose of thiamine on admission (0 or 100 mg) had a significant effect on total neurological signs at baseline in the Asymptomatic At-Risk group [F (1, 156) = 11.18, p = 0.001, partial eta-squared = 0.07]. In the Symptomatic group, the same analysis revealed a marginally significant effect of statim dose [F (1, 33) = 3.80 p = 0.060, partial eta-squared = 0.10] and a significant effect of baseline thiamine pyrophosphate (TPP) [F (1, 33) = 7.66, p = 0.009, partial eta-squared = 0.19]. In other words, statim dose accounted for approximately 7% in the At-Risk group, 10% in the Symptomatic group, and baseline TPP approximately 20% of the variance in total neurological signs at baseline in the Symptomatic group. In all these analyses, assumptions of homogeneity of the variance–covariance matrices were satisfied. While the risk of Type I errors with these multiple posthoc analyses is increased, all these significant effects

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TABLE 1 Summary of baseline characteristics by intervention group

	Asymptomatic at-risk			Symptomatic		
	100 mg/daily	100 mg TDS	300 mg TDS	100 mg TDS	300 mg TDS	500 mg TDS
Gender, *N* (%) male	34/57 (59.6)	38/69 (55.1)	60/102 (58.8)	18/28 (64.3)	16/26 (61.5)	14/21 (66.7)
Indigenous status, *n*/*N* (%) Indigenous	42/57 (73.7)	50/69 (72.5)	67/102 (65.7)	14/28 (50)	10/26 (38.5)	10/21 (47.6)
Age, mean years (SD)	40.5 (11.33)	44.1 (11.2)	41.0 (11.8)	44.6 (11.3)	48.1 (9.3)	48.5 (10.3)
TPP level (nmol/L), mean (SD)	162.9 (58.1)	153.4 (40.2)	160.5 (47.9)	176.1 (58.3)	200.1 (64.7)	158.9 (61.1)
Magnesium (mmol/L), mean (SD)	0.79 (0.21)	0.75 (0.12)	0.75 (0.14)	0.81 (0.23)	0.75 (0.27)	0.75 (0.13)
Days since last thiamine, mean (SD)	91.6 (106.6)	99.3 (107.6)	114.8 (99.0)	60.8 (56.6)	70.1 (82.3)	160.0 (156.0)
BMI, mean (SD)	27.1 (8.2)	26.3 (6.6)	26.3 (6.0)	25.0 (7.7)	25.2 (7.1)	26.5 (5.2)
Education, mean years (SD)	10.06 (2.9)	9.58 (3.4)	11.35 (4.4)	10.84 (3.7)	11.05 (4.0)	11.62 (6.4)
AUDIT-C, mean SD	9.5 (2.1)	9.3 (2.1)	9.6 (2.0)	9.9 (2.5)	10.2 (2.2)	10.4 (2.5)
CogState						
Identification, LogMean (SD)	2.83 (0.1)	2.86 (0.2)	2.83 (0.1)	2.81 (0.2)	2.88 (0.2)	2.88 (0.1)
One back, LogMean (SD)	2.98 (0.1)	3.02 (0.1)	2.98 (0.1)	2.99 (0.03)	2.99 (0.1)	3.03 (0.1)
RUDAS, mean (SD)	25.56 (3.5)	25.28 (3.2)	25.97 (2.9)	25.21 (4.5)	25.07 (2.7)	25.04 (3.1)
Story recall, mean (SD)	20.9 (9.0)	19.0 (9.4)	20.6 (7.6)	22.3 (8.8)	21.2 (8.5)	20.3 (4.8)
Oculomotor abnormality (at randomization), *N* (%) abnormal	3 (5.3)	3 (4.3)	10 (9.8)	24 (85.7)	20 (76.9)	18 (85.7)
Ataxia (at randomization), *N* (%) abnormal	0	4 (5.8)	2 (2)	24 (85.7)	20 (76.9)	16 (76.2)
Confusion (at randomization), *N* (%) abnormal	0	0	0	1 (3.6)	4 (15.4)	4 (19.0)
Oculomotor abnormality (combined variable), *N* (%) abnormal	4 (7)	7 (10.6)	9 (8.9)	17 (60.7)	12 (46.2)	11 (55.0)
Ataxia (combined variable), *N* (%) abnormal	16 (28.6)	14 (21.2)	19 (18.8)	22 (78.6)	17 (68.0)	17 (85.0)
Confusion (combined variable), *N* (%) abnormal	0 (0)	1 (1.5)	1 (1)	1 (3.6)	1 (3.8)	1 (5.0)
WKS diagnosis, *N* (%)	2 (3.5)	0	5 (4.9)	10 (35.7)	11 (42.3)	10 (47.6)
Hospital presentations in last 12 months, mean (SD)	5.1 (8.8)	6.5 (6.2)	5.4 (5.7)	5.6 (5.6)	9.4 (17.6)	7.9 (7.4)
Baseline RUDAS ≤22 indicative of cognitive impairment, *N* (%)	13 (22.8)	12 (17.1)	14 (13.9)	4 (14.3)	4 (15.4)	5 (21.7)
Follow-up RUDAS ≤22 indicative of cognitive impairment, *N* (%)	5 (8.8)	10 (14.3)	11 (11)	4 (14.3)	3 (11.5)	6 (26.1)
Significantly improved at FU, *N* (%)	9 (15.8)	4 (5.7)	8 (8)	2 (7.1)	1 (3.8)	2 (8.7)
Significantly declined at FU, *N* (%)	1 (1.8)	2 (2.9)	5 (5)	2 (7.1)	0 (0)	3 (13)

make physiological sense, and some are associated with medium to large effects.

To determine whether there was a significant improvement in cognition over time, a series of repeated measures *t*-tests were conducted on cognitive outcome measures. These revealed there was a significant improvement in cognition for both the symptomatic and at-risk groups on all measures overall. When separated by dose, there was no clear pattern to suggest the superiority of any of the doses. Asymptomatic At-Risk patients showed significant improvements on the RUDAS and Story Recall at all dosage levels (except

TABLE 2 Cognitive results at 3- or 5-day follow-up for Asymptomatic At-Risk and Symptomatic groups, respectively

	Asymptomatic at-risk					Symptomatic				
	100 mg/daily	100 mg TDS	300 mg TDS	*p*-Value	Partial eta^2	100 mg TDS	300 mg TDS	500 mg TDS	*p*-Value	Partial eta^2
RUDAS	*N* = 59	*N* = 67	*N* = 101			*N* = 29	*N* = 27	*N* = 23		
M (SD)	27.0 (2.4)	26.4 (2.8)	27.0 (3.1)	0.52	0.006	26.3 (3.2)	26.8 (2.7)	25.9 (3.2)	0.39	0.025
Adj. *M* (SE)	27.0 (0.3)	26.6 (0.3)	26.9 (0.2)			26.2 (0.5)	26.8 (0.5)	25.9 (0.5)		
CogState identification (*N*)	*N* = 38	*N* = 48	*N* = 77			*N* = 21	*N* = 18	*N* = 17		
Log mean RT										
M (SD)	2.80 (0.1)	2.84 (0.1)	2.80 (0.1)	0.18	0.02	2.82 (0.1)	2.84 (0.1)	2.83 (0.1)	0.46	0.03
Adj. *M* (SE; 95% CI)	2.81 (0.01; 2.78 to 2.83)	2.83 (0.01; 2.81 to 2.85)	2.81 (0.01; 2.79 to 2.82)			2.85 (0.02; 2.81 to 2.89)	2.82 (0.02; 2.78 to 2.87)	2.82 (0.02; 2.77 to 2.86)		
Arcsine accuracy										
M (SD)	1.44 (0.15)	1.43 (0.16)	1.42 (0.17)	0.62	0.006	1.41 (0.18)	1.34 (0.20)	1.36 (0.23)	0.31	0.04
Adj. *M* (SE; 95% CI)	1.44 (0.03; 1.39 to 1.50)	1.43 (0.02; 1.39 to 1.48)	1.41 (0.02; 1.38 to 1.45)			1.42 (0.04; 1.34 to 1.49)	1.33 (0.04; 1.25 to 1.41)	1.37 (0.04; 1.29 to 1.45)		
CogState One back (*N*)	*N* = 36	*N* = 37	*N* = 68			*N* = 18	*N* = 14	*N* = 14		
Log mean RT										
M (SD)	2.92 (0.13)	2.95 (0.11)	2.93 (0.12)	0.97	0.000	2.96 (0.16)	2.94 (0.12)	2.99 (0.13)	.35	0.016
Adj. *M* (SE; 95% CI)	2.93 (0.01; 2.91 to 2.96)	2.93 (0.01; 2.91 to 2.96)	2.93 (0.01; 2.92 to 2.95)			2.97 (0.02; 2.93 to 3.02)	2.94 (0.03; 2.89 to 3.0)	2.97 (0.03; 2.92 to 3.02)		
Arcsine accuracy										
M (SD)	1.27 (0.16)	1.28 (0.18)	1.31 (0.15)	0.55	0.009	1.30 (0.22)	1.29 (0.20)	1.34 (0.21)	0.66	0.02
Adj. *M* (SE; 95% CI)	1.27 (0.03; 1.22 to 1.32)	1.29 (0.03; 1.24 to 1.34)	1.31 (0.02; 1.27 to 1.34)			1.30 (0.04; 1.21 to 1.39)	1.28 (0.05; 1.19 to 1.38)	1.34 (0.05; 1.25 to 1.44)		
Story recall (*N*)	*N* = 42	*N* = 49	*N* = 67			*N* = 22	*N* = 17	*N* = 18		
Total										
M (SD)	23.5 (8.2)	20.9 (9.1)	24.6 (7.6)	0.057	0.04	24.4 (7.8)	24.5 (5.7)	22.8 (5.9)	0.75	0.011
Adj. *M* (SE; 95% CI)	23.0 (0.8; 21.3 to 24.7)	21.8 (0.8; 20.3 to 23.4)	24.3 (0.7; 23.0 to 25.6)			23.8 (1.0; 21.9 to 25.7)	24.6 (1.1; 22.4 to 26.7)	23.4 (1.1; 21.3 to 25.6)		
Story 1										
M (SD)	13.1 (5.1)	12.2 (5.7)	13.9 (4.5)	0.21	0.02	13.7 (4.1)	13.9 (4.0)	12.4 (3.3)	0.56	0.022
Adj. *M* (SE)	12.9 (0.6)	12.6 (0.5)	13.8 (0.5)			13.2 (06)	14.0 (0.7)	13.0 (0.7)		
Story 2										
M (SD)	10.4 (3.9)	8.8 (4.1)	10.7 (3.8)	0.047	0.04	10.6 (4.4)	10.5 (3.0)	10.4 (3.0)	0.96	0.002
Adj. *M* (SE; 95% CI)	10.2 (0.5; 9.3 to 11.2)	9.1 (0.5; 8.2 to 9.9)	10.6 (0.4; 9.8 to 11.3)			10.6 (0.6; 9.4 to 11.8)	10.6 (0.7; 9.2 to 12.0)	10.4 (0.7; 9.1 to 11.7)		

100 mg TDS was marginally nonsignificant on story recall $p = 0.065$). Symptomatic patients showed a more complex pattern of results with only the intermediate treatment dose of 300 mg TDS demonstrating significant improvements on RUDAS and the intermediate and high doses of 300 mg TDS and 500 mg TDS showing significant improvements on Story Recall. At all dosage levels for Asymptomatic At-Risk patients, accuracy significantly improved on both Cogstate tasks and reaction time significantly improved in some cases (i.e., Oneback RT at 100 mg daily and 100 mg TDS and identification RT at 300 mg TDS only). For Symptomatic patients, accuracy improved on all doses except the highest dose ($p = 0.06$) but reaction time did not significantly improve.

DISCUSSION

This study found no significant difference between the three-dose conditions in either study, namely for either the Asymptomatic At-Risk group or the Symptomatic group. This pattern of results was not what was expected. Possible explanations for these unexpected findings may include loss of power due to a smaller sample size in the symptomatic arm, lack of sensitivity of the cognitive and neurological assessments used, suboptimal timing of the assessments, lack of sufficient treatment duration to elicit an effect, interaction with statim dose effect on admission, or nonlinear effects or ineffectiveness of the treatment.

Due to the uncertainty of causal interpretation associated with the null effects observed in both studies, the significance of these null findings is difficult to describe with certainty and hence requires interpretation with caution. Three general classes of interpretation are presented. Firstly, in view of the all-or-none effect observed in historical pragmatic trials, and the small positive dose-effect in the earlier RCT from our group (Ambrose et al., 2001), across a lower dose range, one possible interpretation is that the therapeutic threshold is lower than targeted by the dose-range used in the current study. This inference is supported by the posthoc analysis which revealed nontrivial effects of statim dose on neurological signs at baseline in both groups and of baseline TPP levels in the Symptomatic group. In other words, it is possible that the single statim dose achieved the therapeutic effect that was to be observed over the duration of this treatment trial.

If there is no benefit in administering a higher dose of thiamine, and if replicated in other randomized trials, such a finding may change clinical recommendations, currently derived from a narrow empirical evidence base, that suggests high dose parenteral thiamine is needed (Galvin et al., 2010; Thomson et al., 2002). Such a pattern of findings would lead to a lower dose regimen, thereby translating to healthcare cost savings. There is separate tentative support for this interpretation. A recent retrospective study evaluating "high dose" (i.e., ≥200 mg twice daily) vs. "low dose" (i.e., <200 mg twice daily) IV thiamine regimens in patients with Wernicke's encephalopathy failed to detect a significant difference in clinical characteristics between the two dosage groups (although an association between higher dose and lower mortality approached but did not reach significance $p = 0.061$ after controlling for potential confounders) (Nakamura et al., 2018). Similarly, another retrospective chart review showed no difference in time to resolution of symptoms for patients who received "high dose" (>100 mg IV daily for at least 1 day) compared to "low dose" (≤100 mg IV daily for at least 1 day) thiamine (Alim et al., 2017). A further, recently completed, blinded, RCT conducted by our group in a metropolitan rehabilitation setting (but not yet published) also failed to demonstrate the benefit of a higher dose regimen on cognitive outcomes (Bowden, S.C.; Scalzo, S.J.; Lloyd-Jones, M.; Bonomo, Y.; McDonough, M. in preparation).

A second alternative interpretation is that our current study lacked adequate design power due to a range of factors, including inadequate treatment duration. It may be that there is a complex temporal interaction between the benefits of lower dose thiamine on acute neurological signs, and the benefits of higher doses on cognitive recovery over longer durations (Scalzo et al., 2014). In Victor and colleagues' long-term study of recovery from the Korsakoff phase of WKS, many patients took weeks or months to show clinical improvement in cognitive status and some, many years (Victor et al., 1989). Such interpretation is supported also by the evidence suggesting a complex cascade of temporal effects associated with thiamine depletion and re-supplementation in animal models (Savage, 2015). A recent case series investigating high dose (≥500 mg daily) thiamine also showed that the duration of high dose thiamine was longer in patients whose symptoms resolved (median = 3 days) compared to those with persistent symptoms (median = 2 days) (Nishimoto et al., 2017). A number of guidelines recommend at least 3 days of treatment with IV thiamine and that treatment should continue for as long as improvement is observed (Pruckner et al., 2019; Thomson et al., 2013; WA Country Health Service, 2019). In addition, a recent literature review reported that it is reasonable to consider a minimum of 72 h of treatment with a high dose as likely to achieve complete resolution of symptoms (Smith et al., 2020). There was variable treatment adherence in our study with the proportion of those receiving all treatment doses ranging from 39% to 93% across the 6 dosage conditions with possible impacts on treatment duration. While the assessment of outcomes at a longer duration might have been useful, this was considered impractical both in terms of the study budget, and logistically due to the short duration of hospital stay for most participants in the current setting.

The third class of interpretation relates to the potentially critical role of other metabolic or physiological factors. For example, the nonadministration of other B vitamins (e.g., vitamins B1, B2, B6, with C, nicotinamide as in Pabrinex) given that some B vitamins may hold synergistic biochemical roles in the nervous system (Calderón-Ospina & Nava-Mesa, 2020). An interaction with magnesium depletion in inhibiting a therapeutic effect of parenteral thiamine might also be considered (Dingwall et al., 2015; McLean & Manchip, 1999; Peake et al., 2013; Traviesa, 1974). Further research is required to examine this complex hypothesis.

Overall, the clinical impact of these research findings is unclear. Nevertheless, these results do support findings from a recent

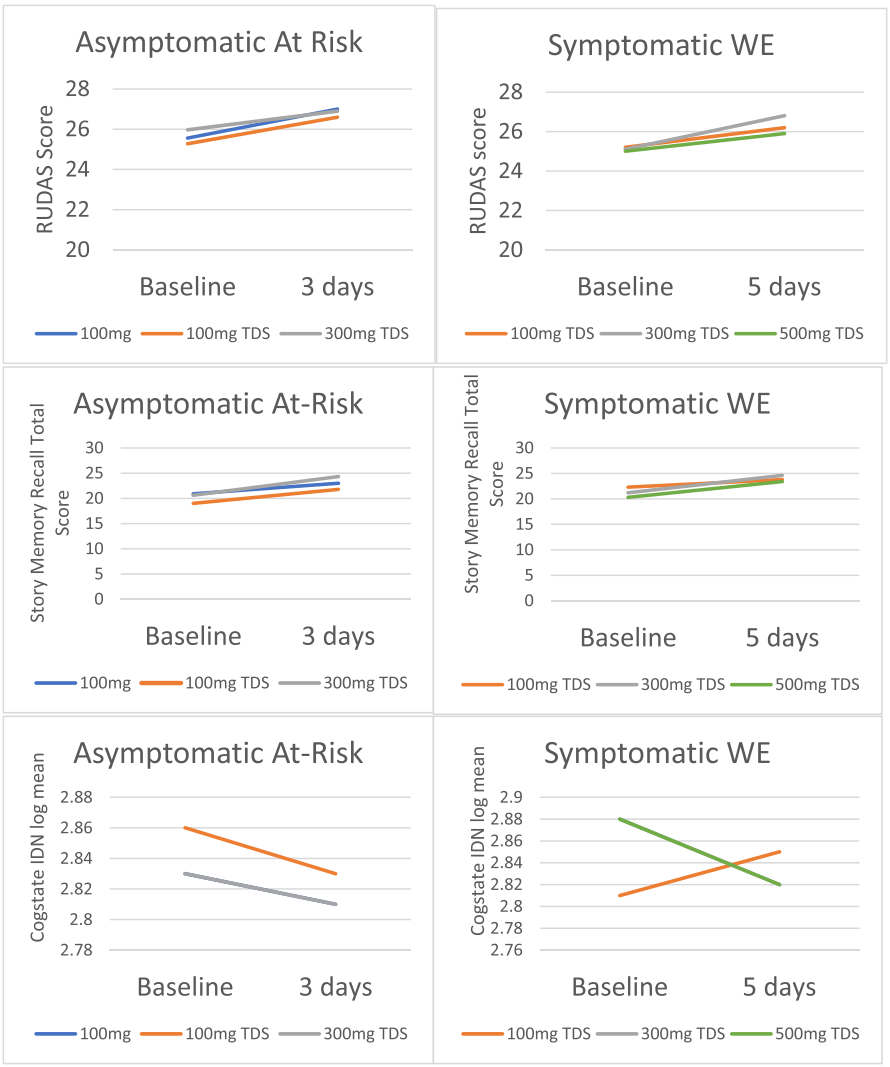

FIGURE 3 Change in cognitive scores baseline to follow-up for each of the study doses (scores on Cogstate IDN log mean identical for 100 and 300 mg TDS for Asymptomatic At-Risk group and for 300 mg TDS and 500 mg TDS for Symptomatic group)

TABLE 3 Logistic regression results for Neurological Symptoms at 3- or 5-day follow-up for Asymptomatic At-Risk and Symptomatic groups, respectively

Neurological measure	Low dose % abnormal	Mid dose % abnormal	Highest dose % abnormal	χ^2 statistic	df	*p*-Value	Nagelkerke R^2	Correctly classified %
Study 1—Asymptomatic at-risk	100 mg/ daily	100 mg TDS	300 mg TDS					
Ataxia	21.2%	18.2%	12.5%	35.63	3	<0.001	0.269	84.3
Oculomotor abnormality	5.9%	9.0%	9.2%	24.85	3	<0.001	0.25	91.5
Confusion	0%	4.5%	0%	12.39	3	.006	0.559	99.5
Study 2—Symptomatic	100 mg TDS	300 mg TDS	500 mg TDS					
Ataxia	53.8%	60.0%	65.0%	8.79	3	0.03	0.157	69.0
Oculomotor abnormality	34.6%	26.9%	35.0%	10.91	3	0.01	0.197	66.7
Confusion	0%	0%	5.0%	10.54	3	0.01	1	100

literature review revealing a similar thiamine dose effect on WE symptoms with varying treatment regimens and that treatment of WE associated with alcohol misuse should be patient-specific, with dose and duration sufficient to mitigate the patient's symptoms (Smith et al., 2020). We tentatively recommend commencing treatment at the lower dose (i.e., Asymptomatic At-Risk 100 mg once daily ivi and Symptomatic 100 mg thrice daily ivi). Where there is no improvement in WE signs or clinical deterioration occurs, reassessment for other comorbidities should be undertaken and clinical findings should be corrected or actively treated with consideration given to further increasing the thiamine dose to the next level (i.e., 100 mg thrice daily ivi or 300 mg thrice daily ivi, respectively). These tentative recommendations should be considered with regard to the limitations outlined below.

The challenges associated with conducting a pragmatic RCT (that resembles usual practice) among typically socioeconomically disadvantaged, culturally and linguistically diverse, alcohol misuse patients were evident and contributed to several study limitations. The rural location and remote domicile of many patients meant that the population pool was somewhat limited and re-presentations to ED were common. While we only included data from individuals once, some participants had presented to the hospital, were treated with parenteral thiamine, and completed assessments including elements of the study protocol (e.g., RUDAS) without being recruited to the current treatment study until a subsequent presentation. Therefore, some participants may have received assessment and thiamine treatment multiple times over the study period thus with unavoidable potential for test familiarity or residual thiamine effects. Nevertheless, the likely impact of test familiarity was considered small given that pilot testing revealed a relative lack of practice effects upon repeat testing (Dingwall et al., 2017). Furthermore, the clinical needs of patients justifiably outweighed research needs, thus those considered too unwell or those not responding to treatment were removed from (or not recruited to) the study. Although removals on medical grounds (identified reasons included: nonresponse to treatment in 1 symptomatic case, sent to ICU, late identification of exclusion criteria (psychosis, suspected brain injury) treatment refusal, due for discharge, anaphylaxis to IV thiamine at the highest dose) only occurred for 15 participants in the Asymptomatic At-Risk study (6 on lowest dose, 6 on intermediate dose, and 3 on highest dose) and 6 in the Symptomatic study (2 on lowest dose, 2 on intermediate dose, and 2 on highest dose), there were also high rates of attrition otherwise and incomplete recruitment across some conditions. This sample attrition together with the inability to recruit and assess severely unwell patients (i.e., those for whom high dose may be most effective) may have attenuated potential treatment effects.

As alluded to, factors related to the timing of assessments and treatment may have also limited our ability to generate conclusive findings. The study protocol gave a window of 36 h from admission (and 24 h from statim dose) for baseline assessment and required blood alcohol concentration to be <0.1% (21.7 mnol/L) prior to recruitment, during which time, treatment with thiamine (by other clinical teams) may have already begun. Furthermore, "baseline" TPP levels were assessed upon admission to ED, rather than at the time of cognitive assessment. In some cases, blood tests were completed after statim dose of thiamine was given and therefore inaccurate as a baseline, thus limiting the reliability and usefulness of some of these data. While average TPP levels were generally within the normal range and ranged from 52 to 322 nmol/L, single case reports have suggested that Wernicke's can be present even with normal TPP (Davies et al., 2011). Only two participants were identified to have TPP below normal levels. While the administration of a statim dose was not randomized and may represent a confounder, the numbers of participants who received a statim dose were similar across each of the dosage groups for both studies. Re-analysis of the cognitive data with stat dose as a covariate did not produce any significant change to the findings and stat dose was not considered a significant covariate in those analyses.

Difficulty with the cross-cultural assessment of cognition may have further limited the current findings. Results showed only 17% of the sample may have been cognitively impaired at baseline (according to RUDAS criteria), indicating either a lack of sensitivity to the cognitive assessments used or a lack of actual cognitive symptoms despite the presence of neurological signs (at least in the symptomatic group). While a delayed recall of the Story Memory Recall Test might have been useful, this was not implemented for the sake of brevity given there is a delayed recall component in the RUDAS and the perceived delicate balance between reliable, comprehensive assessment, versus participant burden, and potential attrition considering the voluntary nature of the study and distinct cultural background of participants. In addition, and contrary to a popular hypothesis, the latent variable analysis in diverse populations including alcohol-dependent participants with a high frequency of WKS suggests that "delayed" memory tests are not more sensitive to anterograde memory impairment than supraspan "immediate" recall conditions (Bowden et al., 2001, 2004; Goette, 2020; Tulsky & Price, 2003). In the same vein, a review of the experimental evidence shows no consistent, precisely replicated support for the "accelerated forgetting" hypothesis of amnesia that is not confounded by methodological variables (Cassel & Kopelman, 2019; Geurts et al., 2015; Mayes et al., 2019). Perhaps an examination of other clinical indicators, such as time to resolution of symptoms or mortality rates (although rare and difficult to assess within the timeframe), might have allowed the inclusion of more unwell patients and revealed important effects (Alim et al., 2017; Nakamura et al., 2018; Nishimoto et al., 2017).

CONCLUSION

The results of this study showed no clear benefit of high dose thiamine over intermediate or lower doses of thiamine for the treatment and prevention of cognitive and neurological abnormalities related to WE (synonymous with acute WKS) over the time interval examined. In the absence of conclusive evidence for the superiority of high dose thiamine, these findings support a recommendation that treatment of alcohol-induced WE should be patient-specific (Smith

et al., 2020) and include an investigation of other confounding comorbidities that may impact thiamine replacement (e.g., hypomagnesemia, sepsis, or other metabolic disturbance).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ENDNOTE

[1] One 'Australian standard drink' is defined as containing 10 g of alcohol, which differs from the U.K. definition (i.e. 8 g or 10 ml of pure alcohol) and U.S. definition (14 g of pure alcohol or 0.6 fl oz).

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