


MLC901 (NeuroAiD II™) for cognition after traumatic brain injury: a pilot randomized clinical trial

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Background and purpose: Treatments to facilitate recovery after traumatic brain injury (TBI) are urgently needed. We conducted a 9-month pilot, randomized placebo-controlled clinical trial to examine the safety and potential effects of the herbal supplement MLC901 (NeuroAiD II™) on cognitive functioning following TBI.

Methods: Adults aged 18–65 years at 1–12 months after mild or moderate TBI were randomized to receive MLC901 (0.8 g capsules 3 times daily) or placebo for 6 months. The primary outcome was cognitive functioning as assessed by the CNS Vital Signs online neuropsychological test. Secondary outcomes included the Cognitive Failures Questionnaire, the Rivermead Post-concussion Symptom Questionnaire (neurobehavioral sequelae), Quality of Life after Brain Injury, Hospital Anxiety and Depression Scale, Modified Fatigue Impact Scale and extended Glasgow Outcome Scale (physical disability). Assessments were completed at baseline and at 3-, 6- and 9-month follow-up. Linear mixed-effects models were conducted, with the primary outcome time-point of 6 months.

Results: A total of 78 participants [mean age 37.5 ± 14.8 years, 39 (50%) female] were included in the analysis. Baseline variables were similar between groups (treatment group, $n = 36$; control group, $n = 42$). Linear mixed-effects models controlling for time, group allocation, repeated measurements, adherence and baseline assessment scores revealed significant improvements in complex attention ($P = 0.04$, $d = 0.6$) and executive functioning ($P = 0.04$, $d = 0.4$) at 6 months in the MLC901 group compared with controls. There were no significant differences between the groups for neurobehavioral sequelae, mood, fatigue, physical disability or overall quality of life at 6 months. No serious adverse events were reported.

Conclusions: MLC901 was safe and well tolerated post-TBI. This study provided Class I/II evidence that, for patients with mild to moderate TBI, 6 months of MLC901 improved cognitive functioning.

Introduction

Traumatic brain injury (TBI) is a leading cause of disability and death in young adults [1,2] and has a significant impact not only on the individual, but also on their family, friends and society [3–5]. TBI is caused

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by external forces directly injuring the brain and/or as a result of rotational forces as the brain moves within the skull. Persistent cognitive deficits have been reported to affect 15–40% of adults post-TBI [6,7]. Most commonly, longer-term deficits are observed in the specific cognitive domains of complex attention (multi-tasking), executive functioning (planning and decision making) and cognitive flexibility (switching quickly between tasks) [6,8]. People can also experience neurobehavioral sequelae (including headaches,

dizziness and noise sensitivity), anxiety, depression and fatigue [7,9]. These deficits can profoundly impact a person's day-to-day functioning, often affecting their ability to return to work, social relationships and quality of life [10,11].

Following TBI, the brain has the ability to restore and regenerate damaged cells and neuronal connections. However, following injury, disturbances in the balance between antioxidant defenses and the production of toxic reactive oxygen species (free radicals) known as oxidative stress can occur, causing secondary injury and hindering recovery. Supplementing the body's natural supply of antioxidants may help to reduce oxidative damage caused by reactive oxygen species and facilitate recovery [12]. Indeed, emerging evidence suggests that antioxidant therapies facilitated stabilization of edema, improved cognitive functioning, neurobehavioral sequelae and decreased mortality post-TBI [13]. MLC901 (NeuroAiD II™) is a traditional Chinese medicine that may help to facilitate the restoration of neuronal circuits through its antioxidant properties, promotion of cell proliferation and stimulation of axonal and dendritic neuronal circuits after TBI [14,15]. In rodent models, MLC901 has been shown to both prevent cell death and to stimulate the generation of new neural cells, connections and pathways [14,15]. Rodents given MLC901 after an ischemic injury showed improved survival, neurological recovery, decreased neurodegeneration and improved cognitive functioning [14,15]. This pilot study aimed to test the safety and effects of MLC901 on cognitive functioning in adult humans after mild to moderate TBI, in addition to secondary outcomes of neurobehavioral sequelae, mood, fatigue, physical disability and quality of life. We hypothesized that MLC901 is safe and well tolerated by people with mild to moderate TBI and has a positive effect on cognitive functioning.

Methods

Study design

This was a pilot, double-blind, placebo-controlled, randomized clinical trial known as BRAIn Injury and Neuroaid Supplementation (BRAINS) performed in the Auckland and Hamilton regions of New Zealand.

Standard protocol approvals, registrations and patient consents

All study procedures were conducted in accordance with good clinical practice guidelines and were approved by the Central Regional Ethics Committee (13/CEN/175)

and the Auckland University of Technology Ethics Committee (14/28). Approval was obtained from the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE, 13/SCOTT/100). Written informed consent was obtained from all participants. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN1261300071 1718).

Participants and procedure

Clinicians based in local hospitals or concussion clinics were asked to identify potential participants and to provide them with brief information about the study. Additionally, advertisements were placed in medical facilities and the local press to facilitate self-referrals. Study processes are outlined in Fig. S1.

Inclusion criteria were: (i) aged 18–65 years; (ii) 1–12 months after mild or moderate TBI and (iii) experiencing cognitive functioning difficulties as indicated by a score of >30 on the Cognitive Failures Questionnaire [16]. Exclusion criteria were: (i) coexisting injury or medical condition, which is severe or unstable, that could adversely impact on the outcome measures, such as spinal cord injury or other severe conditions with life expectancy of <5 years; (ii) severe TBI defined by Glasgow Coma Scale score of ≤8; (iii) current participation in another clinical trial; (iv) dependent on others for everyday activities before the onset of the brain injury; (v) pregnant or breast feeding; (vi) not fluent in English or aphasia/dysphasia that precludes ability to complete the assessments; (vii) known allergy to any of the components of MLC901 or (viii) unknown date of injury. A member of the research team contacted each potential participant via telephone to screen for eligibility. TBI was defined according to World Health Organization criteria as an injury to the brain resulting from external physical forces [17]. TBI was classified as mild based on a Glasgow Coma Scale score of 13–15 and as moderate based on a score of 9–12. Any cases where a Glasgow Coma Scale score was not recorded were classified as mild and unclear cases of TBI were reviewed by a neurologist [17]. Recruitment stopped at 79 participants following identification of significant treatment effects in the interim analysis.

Randomization

Eligible participants were randomized to receive either the MLC901 supplement or placebo using 1:1 minimization randomization [18]. Participants were stratified by study locality (Hamilton/Auckland), time since injury (1–2 months/3–12 months) and sex. The

manufacturer of the supplement and placebo capsules held the group allocation codes until data analysis was completed so that the research team remained blind to group allocation.

Experimental intervention and placebo

MLC901 contains nine herbal components: *Radix astragali*, *Radix salvia miltiorrhizae*, *Radix paeoniae rubra*, *Rhizoma chuanxiong*, *Radix angelicae sinensis*, *Carthamus tinctorius*, *Prunus persica*, *Radix polygalae* and *Rhizoma acori tatarinowii*. The dose was two capsules (0.4 g/capsule) taken orally three times per day for 6 months. Each placebo capsule contained dextrin and magnesium stearate and they were visually indistinguishable from the active pills in terms of the shape/smell and color.

At baseline, 1 and 3 months, participants were given their supply of capsules in blister cards by the researcher. Packaging was visually identical for both groups except for being marked A or B. Participants were advised to take two capsules three times per day. All participants continued to receive standard medical care, with any changes in medical treatment being recorded. If a participant missed one dose, they were advised to take that dose as soon as they remembered. If more than one dose was missed, the participant was advised to take one dose and to continue treatment as usual. Side effects were monitored via telephone calls to participants each week for the first 2 weeks, as well as at each follow-up visit. After the 9-month assessment, participants in the control group were offered a 1-month supply of the MLC901 supplement by a researcher independent of the study team.

Outcome assessment

Following eligibility assessment, an in-person meeting was arranged at the participant's home or other suitable location. Using a repeated-measures design, all measures were administered at baseline, 1, 3, 6 and 9 months to explore the duration and extent of any observed effects.

Primary outcome

Cognitive functioning was assessed by an online neuropsychological test (CNS Vital Signs) [19]. Speed and accuracy on six tests were used to calculate the level of functioning across eight cognitive domains, including verbal and visual memory, complex attention, psychomotor speed, cognitive flexibility, processing speed, executive function and reaction time. Further details of tests and scoring are outlined in Table S2. Raw scores were transformed to standard scores, with a

mean of 100 and SD of 10, based on normative data to account for age and gender effects using an integrated algorithm. Scores <90 indicate below average levels of functioning, with higher scores indicative of better cognitive functioning. CNS Vital Signs has demonstrated good discriminant and concurrent validity with conventional neuropsychological tests [19] and is sensitive to impairments across TBI severity, with evidence of good test–retest reliability [20,21].

Secondary outcomes

The Cognitive Failures Questionnaire [22,23] was included as a self-report measure of attentional lapses. Participants are asked to rate the frequency with which they experience 25 common perception, memory and motor lapses in everyday life, with higher scores indicative of greater attentional lapses. This measure has demonstrated good internal consistency and test–retest reliability [23].

The Rivermead Post-Concussion Symptoms Questionnaire [24,25] assesses neurobehavioral sequelae and consists of two subscales including the RPQ3, which includes symptoms of headaches, dizziness and nausea, and the RPQ13 comprising 13 other common symptoms such as restlessness, noise and light sensitivity, sleep disturbance, blurred vision and balance difficulties. Higher scores indicate greater frequency and severity of symptoms. The two subscales (RPQ3 and RPQ13) have demonstrated good external construct validity and test–retest reliability [24].

Mood was assessed by the Hospital Anxiety and Depression Scale [26]. Participants were asked to rate the extent to which they have been feeling the way described by each item in the past week, yielding separate subscale scores for anxiety and depression. The measure has demonstrated good test–retest reliability [27] and good sensitivity and specificity [28].

Perceived levels of physical, cognitive and psychosocial aspects of fatigue were assessed using the Modified Fatigue Impact Scale [29]. Although initially developed in multiple sclerosis, the measure has been validated in mild to moderate brain injury [30]. Participants were asked to read each statement and to indicate how often fatigue has affected them in each way during the past 4 weeks. A total score is calculated, with higher scores indicative of higher fatigue. This measure has demonstrated excellent test–retest reliability, sensitivity to change and predictive validity [31,32].

The Quality of Life after Brain Injury measure [33] contains 37 items assessing perceived satisfaction with cognitive, self, autonomy in daily life, social, emotional and physical domains of quality of life. Average total subscale scores are converted to a 0–100 scale by

subtracting 1 from the mean and multiplying by 25. Higher scores indicate better quality of life. The measure has demonstrated good internal consistency for the subscale and good test–retest reliability [34].

Physical disability was assessed using the extended Glasgow Outcome Scale [35]. This measure utilizes a structured interview exploring levels of independence. Responses ranged between 1 (dead) and 8 (upper levels of good recovery). The measure has demonstrated good reliability and validity [35].

Statistical analysis

Tests of difference determined if there were any group differences on sociodemographic and clinical variables at baseline. Results expressed as means and SDs across measures at each time-point reveal change over time. Safety and tolerability were assessed by the frequency and nature of any potential side effects recorded. Levels of adherence to the treatment regime were determined based on the number of capsules not taken. All further analyses were conducted by intention to treat.

Repeated-measures analyses using mixed linear regression models adjusting for age, sex, severity of injury, baseline scores, adherence, group and natural recovery over time determined group differences due to group allocation at the primary outcome time-point of 6 months. The participant was used to represent the random effect. Model selection was undertaken with each outcome using standard selection heuristics. Covariates such as education, marital status and occupation were selected based on improving the overall efficiency of the model by pooling the SD observed for the outcome in each arm (MLC901 and placebo) creating an *F*-value. If the mean difference for an outcome between each arm exceeded this *F*-value then it was included as a covariate in the model. Trajectories over time were displayed using smoothed spline from a linear model. Effect sizes were calculated using Cohen's *d*, with small effects classified as $d = 0.2$ – 0.5 , moderate as 0.6 – 1.19 and large as 1.2 – 1.99 [36].

Results

A total of 79 participants were enrolled and randomized into the study. One participant was advised by a clinician to withdraw from the study due to high stress levels. As stress is likely to influence cognitive functioning [37], data collected for this participant were excluded from the analysis. There was no statistical difference in the number of withdrawals between groups ($\chi^2=0.19$, $P = 0.66$). *Post hoc* power

calculations revealed that, with 78 participants, the pilot trial was powered at 80% to observe an effect size of 0.6.

There were no significant differences between the two groups with regard to demographic and other baseline characteristics as shown in Table 1. The majority of TBIs were classified as being mild, with $n = 2$ (3%) injuries classified as moderate in severity. Mean time since injury to enrolment in the study was 148 days (equivalent to 5 months).

Fifty participants (64%) completed the full 9-month protocol (Fig. 1). Eight (10%) participants across the two groups reported side effects during the course of the study. In the intervention group, one participant reported headache, one reported a sore tongue and one reported experiencing itchiness. In the control group, adverse events included difficulty sleeping, headache, itchiness and upset stomach. One further participant in the control group reported experiencing blood in their urine, which, following medical attention, was found to be due to a secondary medical condition. Overall adherence in taking the capsules varied between 84% at 1 month, 89% at 3 months and 85% at 6 months.

Primary outcome

Means and SDs across time-points for all cognitive functioning domains are shown in Table S1. The results of significant regression models are shown in Table 2. Participants randomized to receive MLC901 had significant improvements in complex attention and executive functioning on CNS Vital Signs at 6 months in comparison to controls, with group allocation being independently predictive of complex attention. There was a mean difference of 11.88 for complex attention (>1 SD) and 7.16 for executive functioning, suggesting clinically meaningful improvements at 6 months, with moderate to small effect sizes ($d = 0.6$ and $d = 0.4$ respectively). There were no significant differences between the groups on any other domains of cognitive functioning at 6 months. Using the mean differences observed here ($\alpha = 0.05$) with 80% power, a total sample of 174 participants (87 per group) would be required to determine efficacy of MLC901 on complex attention as part of a full trial. Sensitivity analysis excluding the two cases of moderate TBI from the regression models did not significantly change the results. Group allocation remained a significant independent predictor of complex attention at 6 months ($t = -2.14$, $P = 0.0371$).

Trajectories over time for the cognitive domains of complex attention and executive functioning are shown in Figs 2 and 3. For complex attention, improvements

Table 1 Baseline demographic and medical characteristics of the study participants

	MLC901 group (n = 36)	Control group (n = 42)	Test of difference significance
Males [n (%)]	17 (47.22)	22 (52.38)	P = 0.82
Age (years) [mean (SD)]	38.58 (14.12)	38.40 (15.74)	P = 0.96
Time since injury (days) [median (IQR)]	98.00 (196.75)	94.5 (160.0)	P = 0.59
Ethnicity			
New Zealand European [n (%)]	25 (69.44)	24 (57.14)	P = 0.20
Highest level of education			
Tertiary education or above [n (%)]	12 (33.33)	16 (38.10)	P = 0.81
Employment status			
Employed [n (%)]	19 (52.78)	29 (69.05)	P = 0.17
Marital status			
Married or living with partner [n (%)]	17 (47.22)	15 (35.71)	P = 0.36
TBI severity assessed			
Confirmed severity by GCS score	14 (38.89)	12 (28.57)	P = 0.34
Unclassified severity	22 (61.11)	30 (71.43)	
Mechanism of injury [n (%)]			
Motor vehicle accident	6 (16.67)	7 (16.67)	P = 0.94
Assault	12 (33.33)	13 (30.95)	
Fall	14 (38.89)	15 (35.71)	
Hit by object/other	4 (11.11)	7 (16.67)	
Other injuries sustained			
Yes [n (%)]	19 (52.78)	18 (42.86)	P = 0.50
Prior TBI			
Yes [n (%)]	17 (47.22)	27 (64.29)	P = 0.19
Baseline cognitive functioning level			
Below average	21 (58.33)	22 (52.38%)	P = 0.60

GCS, Glasgow Coma Scale; IQR, interquartile range; TBI, traumatic brain injury.

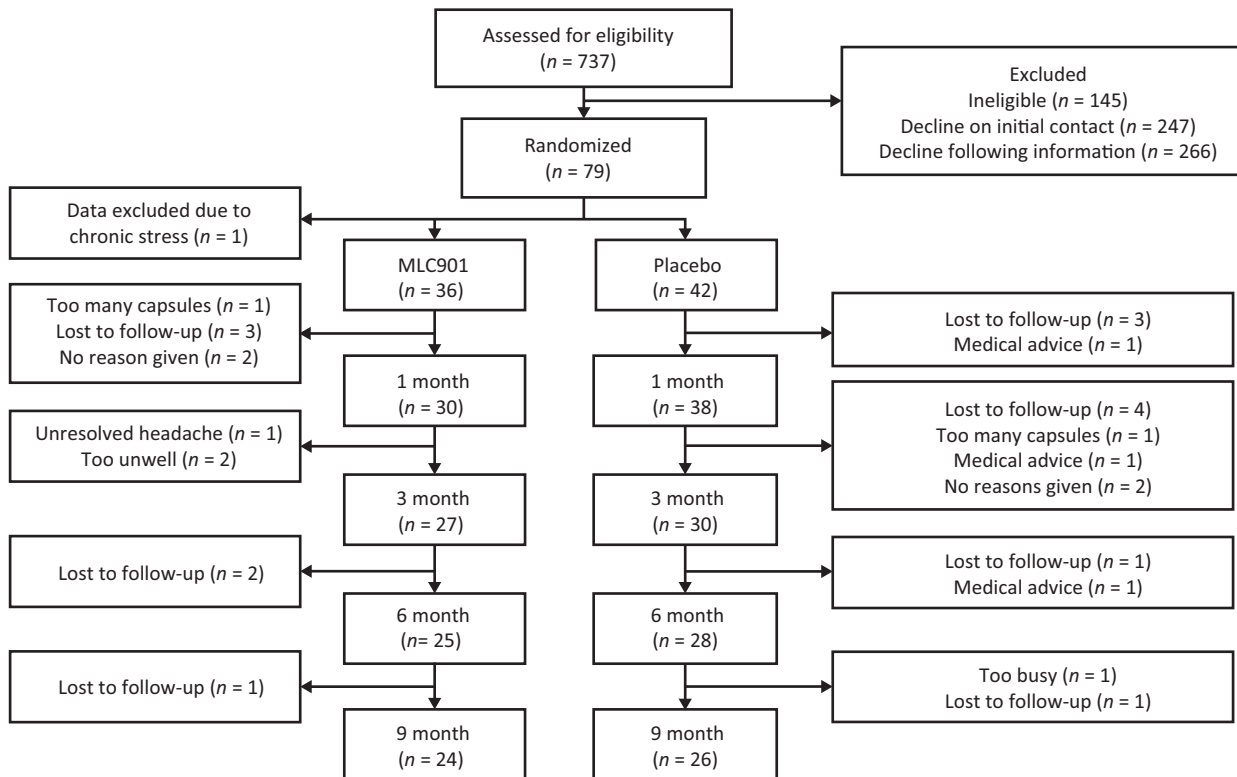
**Figure 1** Consort diagram of participants.

Table 2 Significant linear regression models of cognitive outcomes at 6 months

	Estimate	Standard error	P
Complex attention			
Intercept	91.14	8.36	0.0000
Education	13.38	5.92	0.0238
Occupation (manager)			
Community worker	-22.04	9.59	0.0214
Laborer	-9.48	9.73	0.3320
Technician	-4.88	6.79	0.4715
Machine worker	-15.58	10.02	0.1188
Sales	-7.97	11.63	0.4902
Marital status (in a relationship)	10.59	5.29	0.0455
Time since intervention			
1 month	7.64	1.81	0.0000
3 months	7.58	2.09	0.0003
6 months	8.58	2.47	0.0005
Group allocation	-10.13	4.90	0.0385
Executive functioning			
Intercept	102.40	8.55	0.0000
Sex (male)	-8.14	4.24	0.0549
Education (tertiary)	11.27	4.07	0.0056
Current employment (employed)	-6.67	4.21	0.1141
Mechanism of injury (assault)			
Fall	-12.33	4.79	0.0102
Hit by object	-7.99	6.28	0.2041
Traffic incident	-12.78	6.26	0.0414
Time since intervention			
1 month	9.73	1.66	0.0000
3 months	8.90	1.79	0.0000
6 months	12.74	1.99	0.0000
Group allocation	-10.13	4.90	0.1527
Quality of life (cognition domain)			
Intercept	44.22	9.33	0.0000
Ethnicity (European)			
Maori	-10.59	6.24	0.0891
Asian/other	-7.77	9.14	0.3953
Occupation (manager)	-22.04	9.59	0.3320
Community worker	-9.48	9.73	0.3320
Laborer	-4.88	6.79	0.4715
Technician	-15.58	10.02	0.1188
Machine worker	-7.97	11.63	0.4902
Sales	10.59	5.29	0.0455
Marital status (in a relationship)	-10.53	6.15	0.0873
Time since intervention			
1 month	10.48	1.99	0.0000
3 months	7.69	2.23	0.0006
6 months	11.08	2.57	0.0000
Group allocation	14.31	5.61	0.0108

were observed in the MLC901 group that were cumulative over time, whereas the control group remained relatively stable. For executive functioning, improvements were observed for both groups with improvement accelerated in the MLC901 group. Improvements in cognitive functioning slowed between 6 and 9 months following cessation of treatment.

Secondary outcomes

Both groups showed improvements over time across all secondary outcomes. There were no significant differences between the groups on the neurobehavioral sequelae of mood, fatigue and overall quality of life at the $P < 0.05$ level across time-points. As shown in Table 2, participants receiving MLC901 showed significant improvements on the cognitive domain of quality of life with a mean difference of 1.62; however, the effect size was considered small ($d = 0.1$).

Discussion

The findings provide initial evidence that MLC901 may help to facilitate neural recovery on complex attention and executive functioning following TBI, with small to moderate effect sizes. Few side effects were reported by participants, supporting the safety and tolerability profile of MLC901 post-TBI. There were no significant differences between the groups at follow-up for self-reported cognitive failures, neurobehavioral sequelae, fatigue, mood, physical disability or overall quality of life.

Complex attention and executive functioning are the most common areas of cognitive functioning to be affected post-TBI [6,8]. Significant improvements on these two domains suggest potential clinical utility of MLC901 post-TBI. Trends in improvement in complex attention and executive functioning in the MLC901 group were observed at 3 months, becoming significant at 6 months. This suggests a cumulative and consistent treatment effect, with rate of improvement declining following cessation of treatment. The findings of improved cognitive functioning following treatment with MLC901 support the results of experimental trials of MLC901 on cognitive functioning in rodents [14,15]. The impact of MLC901 on cognitive functioning was strengthened by significant differences observed in both the neuropsychological test and the self-reported cognitive domain of quality of life. The lack of a significant difference on the self-reported measure of attentional lapses (Cognitive Failures Questionnaire) may reflect the focus of this measure on memory and motor lapses rather than complex attention, executive function or impact of these cognitive difficulties on everyday life.

There was no significant difference in post-concussion symptoms, mood, fatigue, physical disability or other domains of quality of life. The lack of significance for mood and disability is likely to reflect that at baseline, scores for both anxiety and depression were in the normal to mild range. Levels of physical functioning indicating that people were functioning

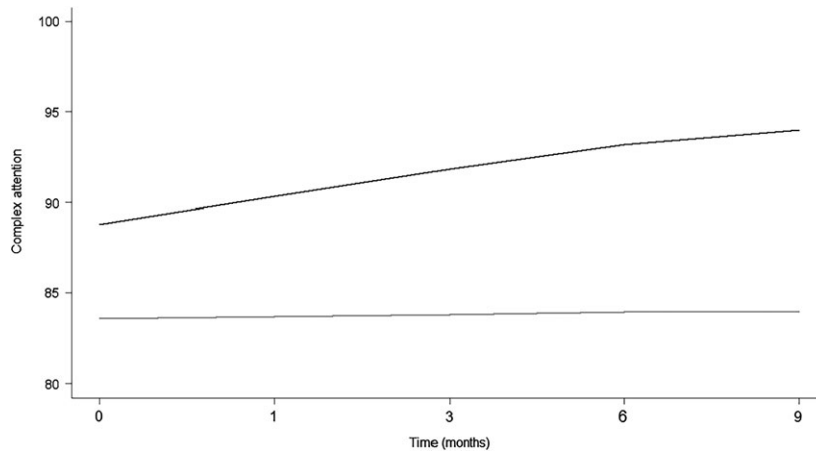


Figure 2 Trajectories of complex attention over time between groups. Grey line, control; black line, MLC901.

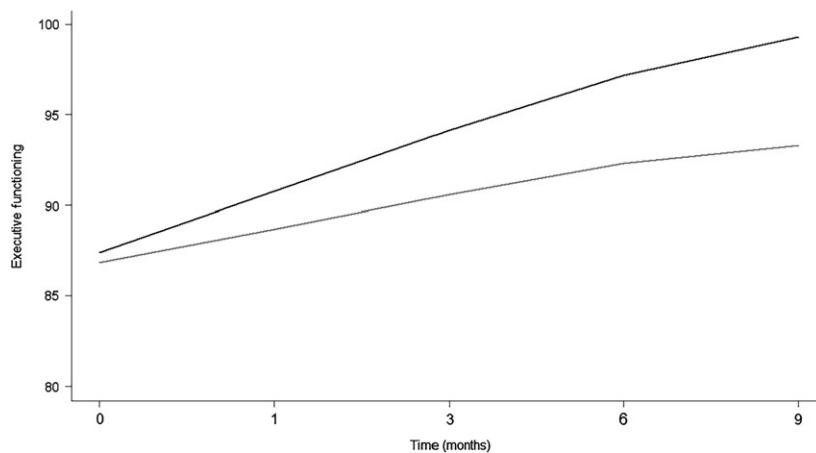


Figure 3 Trajectories of executive functioning over time between groups. Grey line, control; black line, MLC901.

independently made it unlikely that any treatment effect would be observed. Improvements in neurobehavioral sequelae have been observed using other antioxidant treatments although research remains limited [13]. It may be the case that changes have been observed for specific symptoms but are obscured by use of the total symptom score. Analysis by symptom rather than by total symptom severity may be worthy of further exploration.

The brain has been demonstrated to be highly plastic following a TBI with continued improvements observed over the year following injury [6]. Indeed, a key predictor of outcome across both groups was time, indicative of a process of natural recovery. Group allocation was an independent predictor of complex attention, suggesting that MLC901 further facilitates the natural recovery process. As effects were sustained at 9 months following cessation of treatment, this supports an ongoing treatment effect; However, it remains unclear how long improvements may

be sustained. Participants were recruited within 12 months post-injury as it is more likely that the anti-inflammatory and antioxidative effects of MLC901 will affect recovery in the early phase post-injury and evidence supports efficacy up to 12 months post-injury [38]. However, many participants did not enter the trial until 5–6 months post-injury and it remains unclear if earlier administration of MLC901 may further increase the treatment effect or whether there are treatment effects for cognitive difficulties sustained many years following TBI.

Recruitment of participants proved challenging with many participants citing the need to take capsules three times per day over a 6-month period as a barrier to participation, as well as a reason for withdrawal. Adherence was also reported to be challenging, particularly within the context of cognitive difficulties experienced. Condensing the dosages into once or twice daily administration may facilitate recruitment and adherence [39]. Additionally, aids to support memory

could be integrated into the protocol to support adherence. For example, adherence has been found to be increased when medications are taken at the same time and integrated into daily routines [39].

Only 3% of participants had sustained a moderate TBI and findings need to be interpreted with caution for this population. A limitation of the study is that safety and effects of MLC901 remain unknown for those who have experienced a severe TBI. Although few adverse events were reported, one person in the intervention did withdraw from the study due to persistent headaches. It is unknown whether or not this was directly attributable to the MLC901 and headaches should be specifically monitored as part of a full trial. The findings suggest that MLC901 is safe and well tolerated and may help to improve complex attention and executive functioning following mild to moderate TBI. A phase III randomized controlled trial is required to determine effectiveness.

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Disclosure of conflicts of interest

The study was funded by Moleac Pte Ltd, Singapore, who manufacture the MLC901 supplement. The study was designed and conducted independently by the research team. The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Outline of study processes.

Table S1. Means and SDs for the outcome measures across time-points.

Table S2. Test descriptions and computation of domain scores.

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