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Original article

The effect of NeuroAiD™ (MLC601) on cerebral blood flow velocity in subjects' post brain infarct in the middle cerebral artery territory

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ABSTRACT

Background: Stroke is the third common cause of mortality and the most common cause of morbidity in adults. MLC601 (NeuroAiD™) is a treatment indicated for post stroke recovery. An increase of impaired cerebral blood flow may be an important parameter for recovery processes. The aim of this study was to investigate the effect of MLC601 on cerebral blood flow velocity as an indirect evidence of cerebral blood flow increase in post stroke subjects.

Methods: The mean change in cerebral blood flow velocity in the MLC601 treatment group (15.9) was significantly increased ($p=0.009$) compared to the placebo group (9.6). Subjects in the treatment group also showed a significant difference in the mean rank of modified ranking scale ($p<0.001$) and mean change of the Barthel Index: 36 vs. 29 in the placebo group ($p<0.001$).

Results: The mean change in cerebral blood flow velocity in the MLC601 treatment group (15.9) was significantly increased ($p=0.009$) compared to the placebo group (9.6). Subjects in the treatment group also showed a significant difference in the mean rank of modified ranking scale ($p<0.001$) and mean change of the Barthel Index: 36 vs. 29 in the placebo group ($p<0.001$).

Conclusion: This is the first study suggesting that treatment with MLC601 may increase cerebral blood flow in stroke subjects. This may be mediated by an effect on stimulating microcirculation, an important process contributing to neuroplasticity in the central nervous system. This effect on cerebral blood flow may be associated with improvement in measures of functional recovery.

1. Introduction

Stroke is the third common cause of mortality and is the most common cause of long-term disability in adults. Ischemic and hemorrhagic stroke account respectively for 82% and 18% of all strokes in Iran [1]. Cerebral infarct leads to a localized death of brain tissues. Emergency treatment for ischemic stroke is essentially limited to thrombolysis [2] and is only applicable to less than 1% of patients in Iran due to general limits in eligibility criteria, hurdles in patient care, high cost and lack of health insurance coverage for this intervention [3]. 75% of survivors are affected by serious disabilities, which depend on the size and the location of the injury in the brain and may affect all neurological functions: motor, sensory and cognitive.

The sudden interruption or decrease of the blood supply results in oxygen and energy deprived neurons in the ischemic core zone to cease function and show rapid sign of structural damage within minutes resulting in neuronal death [4]. Typically the core fails to regain its fine dendritic structure after reperfusion. In the penumbral zone, the blood flow increases towards the midline as tissues are supplied by other artery system left unblocked during the stroke and some loss of dendrites will reverse when reperfusion occurs. The brain has a natural ability to recover function [5], as some loss reverses in the penumbra and later through neuroplasticity processes; the brain establishes new synaptic connections and modulates the strength of existing connections [6]. These processes which are supported by an efficient microcirculation in the brain tissues as well as cell proliferation and migration towards the periphery of the injured tissues and the formation of new neuronal circuits [7]. There is a need for new treatments for stroke rehabilitation to support these processes and help patients achieving a more complete recovery.

MLC601 (NeuroAiD™, Moleac Pte.Ltd, Singapore) is a TCM (Traditional Chinese Medicine), which is used extensively in Asia to facilitate recovery after stroke [8]. It combines nine herbal compounds (including Radix astragali, Radix salviae miltiorrhizae, Radix paeoniae

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rubra, Rhizoma chuanxiong, Radix angelicae sinensis, Carthamus tinctorius, Prunus persica, Radix polygalae and Rhizoma acori tatarinowii) and 5 animal components (including Hirudo, Eupolyphaga seu steleophaga, Calculus bovis artifactus, Buthus martensii and Cornu saigae tataricae). Previous clinical studies have demonstrated that MLC601 may enhance recovery post stroke. A large double-blinded, placebo-controlled, randomized clinical trial at the acute stage of brain infarct is ongoing to assess the benefits on MLC601 when initiated within 72 h post stroke [9]. MLC601's safety profile is well established in healthy volunteers, acute and chronic stroke patients [8,10,11].

Recent pharmacological data has demonstrated that MLC601 treatment increases survival cell rate, prevents neuronal death, reduces infarct volume, and decreases functional deficits in rodent stroke models. MLC601 showed neuroprotective effect against oxidative stress and excitotoxicity. MLC601 also exerts effects on neuroplasticity during stroke recovery including through Brain-Derived Neurotrophic Factor (BNDF), a major neuronal growth factor. MLC601 has been demonstrated to stimulate neurogenesis, neurites' outgrowth and synaptogenesis [12], which participate in the formation of new neuronal circuitries.

To further understand the role of MLC601 in clinical neuroplasticity, we decided to investigate the effects of MLC601 on cerebral blood flow velocity within the territory of middle cerebral artery.

2. Methods

2.1. Study design and subjects

This was a single centre, double-blinded, placebo-controlled, and randomized study. The subjects were recruited from Ahvaz Golestan Hospital in Iran from April 2009 until March 2010.

All subjects were randomized to either group A (MLC 601, 4 capsules 3 times daily) or group B (placebo (talc), 4 capsules 3 times daily, 3 months) based on a one-to-one allocation according to a computer generated randomization list prepared by an appointed staff. Through the study, patients and all active assessors – i.e. TCD examiner, BI and mRS raters – were unaware about the treatment allocation of group A and B. All subjects were given standard antiplatelet (aspirin) treatment (80 mg twice a day). The inclusion and exclusion criteria are listed below.

2.2. Inclusion criteria

(1) Adults between 60 and 80 year old
(2) Acute brain infarct in the territory of MCA (large-artery atherosclerosis, subtype 1 of TOAST classification [13]) within one week of randomization confirmed by neuroimaging (CT scan or MRI)
(3) Hospitalization within 24 h of stroke
(4) Written informed consent obtained from the subject or legal representative

2.3. Exclusion criteria

(1) Intra-cerebral hemorrhage or hemorrhagic conversion
(2) History of previous stroke or evidence of pre-existing stroke on brain imaging
(3) Inability to swallow
(4) Significant systemic disease: Chronic Obstructive Pulmonary Disease, severe asthma, CO_2 narcosis, renal failure, severe congestive heart failure, uncontrolled hypertension, uremia, cirrhosis, psychosis, dementia
(5) Other brain pathologies (i.e. primary brain tumors, metastasis or infectious lesions)
(6) Participation in another clinical trial within three months of inclusion

2.4. Outcome measures

The primary efficacy endpoint was the change in cerebral blood flow velocity, defined as the difference in mean flow velocity (MFV) in cm/s of the bilateral middle cerebral artery recorded before treatment initiation and at 3 months using transcranial Doppler ultrasonography (Multi Dop X4 system, DWL: Germany). One appointed examiner in the same sonology laboratory and identical environment temperature did all TCD evaluations. Before examination, body temperature and instant blood sugar were checked by using a conventional thermometer and a blood glucometer appliance (CLEVER CHEK® TD-4230). The study was postponed until controlling the condition whenever fever and/or a blood sugar >200 mg/dl were detected. For all subjects, TCD evaluation was done in the depth of 55–60 mm through the temporal window.

The secondary end points were the Barthel index (BI) score and modified Rankin scale (mRS) [14,15], scales to measure performance and autonomy level in basic activities of daily living. mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke and runs from 0 to 6, from perfect health without symptoms to death. BI scale consists of 6 grades and the maximal score is 100. A score of 65 in Barthel index is a pivotal score at which patient disability changes from assisted independence to dependency for essential personal care [16,17].

2.5. Other tests

Enrolled subjects were selected from stroke patients admitted to Ahvaz Golestan Hospital who fulfilled the inclusion and exclusion criteria. All underwent the routine neurology ward investigations, including Chest X-ray, ECG, blood biochemical and lipid profile tests, coagulation status and urine analysis.

The study was approved by medical ethics committee of Ahvaz Jundishapur University of Medical Sciences (registration number: p/8/20/759) as well as it was registered in the Iranian representative of World Health Organization clinical trial registration system (IRCT, available at www.irct.ir under registration number: IRCT138901193663N1).

2.6. Sample size

This is primarily a pilot study as there have been very few studies using the mean flow velocity as an outcome measure of treatment outcome in sub acute stroke patients. The sample size was determined based on an a priori power analysis that indicated that 40 participants in each group would provide a power of 80%.

2.7. Statistical analysis

The data were statistically analyzed with SPSS 13. Kolmogrov–Smirnov Z was used to check whether variables are normally distributed. Baseline variables were compared using a two-group *t* test and *U* Mann–Whitney test for continuous variables and chi-square test for categorical variables. For efficacy variables, comparisons were made between the two groups at baseline and the end of treatment. Independent *t* test (for MFV) and *U* Mann–Whitney test (for BI and mRS) were used to compare variables in each group at baseline and at completion of treatment. Paired *t* test, Wilcoxon test and Sign test were used respectively to compare MFV, BI and mRS, before and after treatment. A *p*-value less than 0.05 was considered as the level of significant difference in all tests.

3. Results

3.1. Subject flowchart

Of the 166 subjects screened, 80 were enrolled in this study: 40 received MLC601, and the other 40 placebo (Fig. 1). 68 subjects

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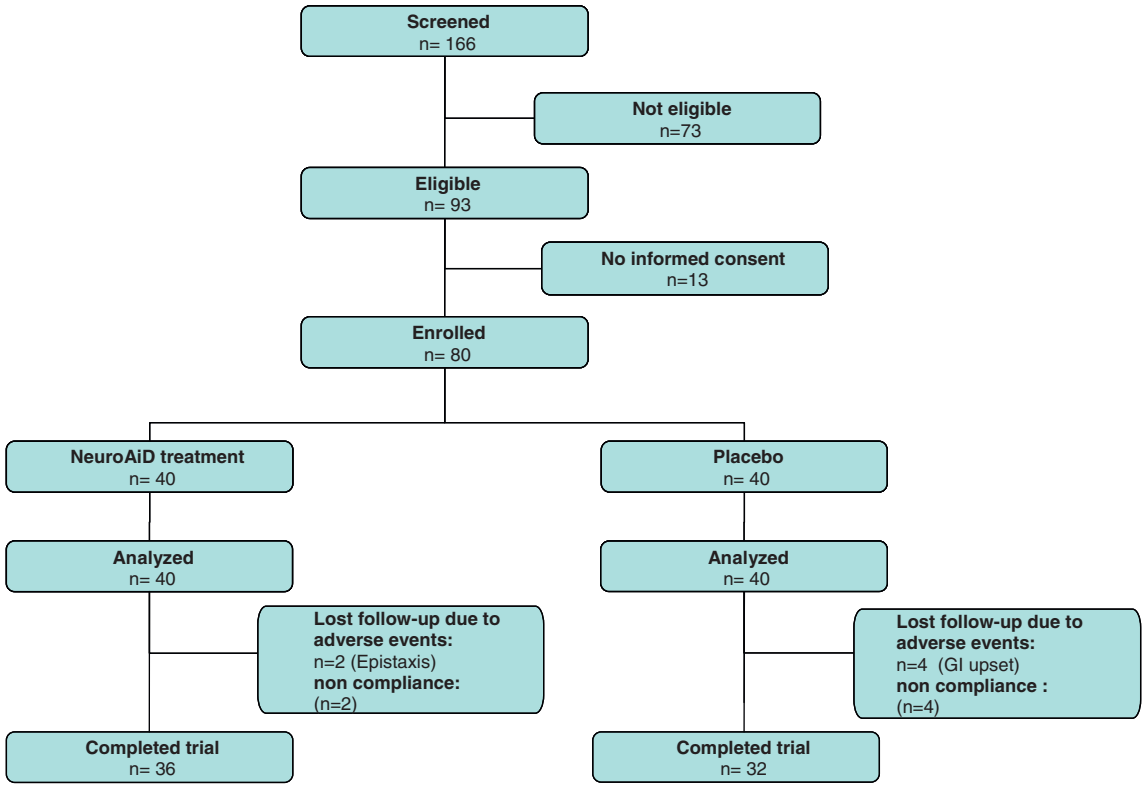

Fig. 1. Subject flowchart.

completed the study, 36 in the MLC601 group and 32 in the placebo group; 2 subjects in the MLC601 group and 4 subjects were lost to follow-up due to adverse events.

Subject compliance information was available for 74 subjects: 2 subjects in the MLC601 group and 4 subjects in the placebo group were reported to be non-compliant. Since the change in baseline is the primary outcome, a per protocol analysis was done.

3.2. Baseline characteristics

The MLC601 and control groups had similar baseline characteristics (Table 1). The subjects were Caucasian, elderly, predominantly male and have similar risk factors. The baseline mean flow velocity, BI and mRS did not differ significantly between groups.

3.3. Efficacy results

3.3.1. Primary endpoint: the mean flow velocity

At baseline, before MLC601 treatment, there was no significant difference between the two groups ($p = 0.822$). Both groups recorded a significant increase in the mean flow velocity (MFV) between baseline and the 3rd month; In the MLC601 group, the mean flow velocity, before and after treatment, was respectively 42.5 ± 9.0 and 58.4 ± 6.4 ($p<0.001$). In placebo group, the MFV also increased from 43.0 ± 11.6 to 52.6 ± 10.3 ($p<0.001$). However, the change of MFV in MLC601 group of 15.9 is significantly higher than the increase of 9.6 in the placebo group ($p = 0.009$) (Table 2).

3.3.2. Secondary endpoint: the Barthel Index

The Barthel Index is a reliable disability scale for stroke survivors [18]. The MLC601 treatment group showed a statistically significant increase in mean BI: 35 ± 7 before treatment vs. 71 ± 7 after treatment ($p<0.001$). In the placebo group, the BI also significantly increased from 36 ± 7 to 65 ± 7 ($p<0.001$). The increase of 36 points in the treatment group is significantly higher than the 29 points recorded in the control group ($p<0.001$) (Table 3a). Accordingly, mRS improved in both groups in comparison to the baseline ($p<0.001$) but MLC601 group had a significantly lower mean rank of mRS (28.4 vs. 41.3), i.e. better function, than placebo group after treatment.

Table 1
Baseline participant characteristics.

Characteristics	MLC601 group ($n=36$)	Placebo group ($n=32$)	p-value
Demographics			
Age, years	70.80 ± 6.31	72.37 ± 5.97	0.298
Sex			
Male	25 (69)	23 (72)	0.826
Female	11 (31)	9 (28)	0.826
Race			
Caucasian	36 (100)	32 (100)	
Medical history: risk factors			
Hypertension	23 (64)	19 (59)	0.702
Diabetes mellitus	9 (25)	10 (31)	0.521
Hyperlipidemia	7 (20)	10 (30)	0.262
Ischemic heart disease	9 (25)	6 (19)	0.576
Drug history			
Anti-platelet	8 (22)	6 (19)	0.724
Statin	6 (17)	6 (19)	0.822
Stroke details			
Site of stroke			
MCA	36 (100)	32 (100)	
Side of hemiplegia			
Left	19 (53)	20 (62)	0.418
Right	17 (47)	12 (38)	0.418
Mean flow velocity	42.45 ± 8.96	43.02 ± 11.64	0.822
Barthel Index score	35.22 ± 7.27	36.12 ± 7.26	0.611
Modified Rankin Scale	4.50 ± 0.50 (4.5) [a]	4.43 ± 0.56 (4)[a]	0.380

Values presented are either means $\pm$ SD or number of subjects in subgroups with percentages in parentheses. MCA: Middle cerebral artery.

[a] Values for modified Rankin scale are means $\pm$ SD with median in parentheses.

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Table 2
Mean flow velocity.

Intervention	*N*	Age (mean ± SD)	Mean flow velocity (mean ± SD)			*p*-value[a]
			Before	After	Delta	
MLC601	36 M: 25 F: 11	70.80 ± 6.31	42.45 ± 8.96	58.43 ± 6.49	15.98 ± 7.14	<0.001
Placebo	32 M: 23 F: 9	72.37 ± 5.97	43.02 ± 11.64	52.64 ± 10.31	9.62 ± 5.78	<0.001
p-value[b]		0.298	0.822	0.009		

N: number.
[a] Before–after analysis of the mean flow velocity of each group in a 3 months interval.
[b] Comparison of means in two groups (MLC601 and placebo), before and after 3 months.

3.4. Exploratory analysis

Using a Barthel Index score of 65 as a cut-off for the level of desired dependency in this study, 69.4% of subjects reached assisted independency level in the treatment group vs. 18.7% of subjects in the control group ($p<0.001$) (Table 3b).

3.5. Safety data

In MLC601 group, there were two cases of non-traumatic epistaxis requiring the use of vasoconstrictor tampons. In placebo group, there were four cases of GI upset. These six subjects left the study. No other adverse events were reported.

4. Discussion

The first objective of this study was to determine whether MLC 601 had an impact on the increase of the cerebral blood flow velocity and whether this could serve as a surrogate marker of MLC601 effect in clinical practice. This study shows statistically significant differences in the effect of MLC601 in increasing the cerebral blood flow velocity of post brain infarct subjects. Increased cerebral blood flow velocity in TCD measurement may be interpreted as a sign of increased cerebral blood flow and/or vascular narrowing (i.e. vasospasm or stenosis). Nevertheless in the latter, worsening of clinical situation or at least insignificant improvement in the functional state of patient is expected. As it was mentioned in the results and will be discussed further in this section, we found a significant improvement in the level of independency in patients who received MLC601 in comparison to placebo. Such a finding is not in favor of occurrence of vascular narrowing, although cannot rule out it thoroughly.

Taking it for granted that our findings are resulted from increase in cerebral blood flow, it should be noted that cerebral blood flow cannot be measured directly by means of TCD flow velocity measurements, however their changes are proportionately related, providing the investigator keeps the same angle of insonation and perfused territory. Therefore, MFV could be interpreted as an indirect evidence of the effectiveness of a certain therapy on increasing the brain tissue perfusion [19]. At a constant cerebral blood volume, the increase of the cerebral blood flow indicates a change in the vascular resistance of the microcirculatory vessels, hence suggesting an angiogenesis activity. Late stage post brain infarct recovery may be largely explained by neuroplasticity processes in which structure and function of synaptic circuitries are supported by local microcirculation within 30 μm from the nearest neighbouring neurons [7,16].

Angiogenesis and neurogenesis mechanisms are linked and have similar mediators; neurons, glial cells and vascular elements interact in the neurovascular unit [17]. Stimulating angiogenesis and microcirculation present an interesting strategy to enhance the neuroplasticity in post brain-infarct patients. MLC601 has been demonstrated to stimulate neurogenesis [12] and this research suggests that angiogenesis may also be triggered. Furthermore, at the acute stage of stroke, the formation of new vessels has been identified in the penumbra of the ischemic zone [20]; a possible role of MLC601 in the reperfusion of salvageable tissue during the acute and sub-acute stage of tissue injury would need to be investigated in acute clinical trials by assessing the variation of mean flow velocity in randomized subjects.

The Barthel Index score of subjects is significantly higher after MLC601 treatment; the BI increases with a factor 2 with a mean final post-treatment value of 71. As mentioned before, modified Rankin scale improved in accordance to BI and confirmed a better functional improvement after MLC601 treatment. There are two previous studies showing that MLC601 may be beneficial and facilitate post stroke recovery [8,9]. Our results in functional outcome are in line with these studies. In a recent randomized pilot study by using more detailed rehabilitation evaluation scales that MLC601 was started within one month after stroke onset for 8 weeks, investigators did not find significant effect of MLC601 rather than placebo but they reported a positive trend in their exploratory analysis after MLC601 treatment, as well [21]. The difference between our findings with them may be

Table 3a
Barthel index.

Intervention	*N*	Age	Barthel Index			*p*-value[a]
			Before	After	Delta	
MLC601	36	70.80 ± 6.31			35.89 ± 7.97	<0.001
	M: 25		35.22 ± 7.27	71.11 ± 6.55		
	F: 11		(35, 5)	(70, 10)		
Placebo	32	72.37 ± 5.97			28.59 ± 6.20	<0.001
	M: 23		36.12 ± 7.26	64.71 ± 7.06		
	F: 9		(35, 9)	(65, 5)		
p-value[b]		0.298	0.459	<0.001		

Values presented are means ± SD with median and interquartile range in parentheses for BI scores.
N: number.
[a] Before–after analysis in Barthel Index of each group in a 3 months interval.
[b] Comparison of two groups (MLC601 and placebo), before and after 3 months.

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Table 3b
Barthel Index dependency.

Intervention	*N*	Undesirable dependency (Barthel Index<65)	
		Before	After
MLC601	36 M: 25 F: 11	36 (100%)	11 (30.6%)
Placebo	32 M: 23 F: 9	32 (100%)	26 (81.3%)
p-value[a]		–	<0.001

Values presented are number of subjects in treatment groups with percentages in parentheses.
N: number.
[a] Comparison of two groups (MLC601 and placebo), before and after 3 months.

partly due to the time of starting the treatment after stroke onset and their shorter period of treatment and follow up.

Furthermore, 69.4% of our subjects treated with MLC601 reach a score superior to 65 in their BI score comparing to only 18.7% of subjects receiving placebo having this level of rehabilitation. However, the small sample size of our study did not allow to correlate the mean flow velocity increase with the improvement of functions of daily living. A larger study with a full assessment of recovery in neurological disabilities and functional scales as well as direct measurement of global and regional cerebral blood flow by means of positron emission scanning may be necessary to establish such a correlation.

There are some study limitations: this study was only conducted on cerebral infarction within the territory of middle cerebral artery; the sample size of 80 subjects is not sufficient to draw any definitive Conclusions and MFV alteration can be considered only as an indirect evidence of cerebral blood flow changes. Both cerebral blood flow velocity and Barthel Index score are significantly improved but the sample is not sufficient to determine a strict correlation between the cerebral blood flow velocity restoration and the functional recovery. Moreover, note that scales such as BI and mRS evaluate functions and related grade of dependency, but the quality of life cannot be assessed by them. Therefore, authors propose to consider quality of life evaluation in upcoming trials with MLC601.

Future larger trials are necessary for confirming the effect of MLC601 on the cerebral blood flow and assessment of the functional recovery, neurological diseases reduction, and activities of daily living.

5. Conclusion

This study shows that MLC601 increases the cerebral blood flow velocity in post brain infarct subjects. Despite a limited sample size we showed that the cerebral blood flow velocity increase is significantly higher in MLC601 group than in control group. The restoration of the microcirculation plays a role in enabling remapping processes of neuroplasticity and might play a role in preventing neuronal death in penumbra at sub-acute stage of brain infarction. Patients in the treatment group recorded a significant improvement in activities of daily living. A larger clinical trial with direct measurement of cerebral blood flow would be required to assess the correlation between the increase in cerebral blood flow and functional recovery.

6. Learning points

- Stroke is the third common cause of mortality and the most common cause of morbidity in adults. MLC601 (NeuroAiD™) is a treatment indicated for post stroke recovery.
- The aim of this study was to investigate the effect of MLC601 on cerebral blood flow increase in post stroke subjects.

Disclosure statement

The authors have no conflict of interest to declare.

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