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DLBS1033 treatment for ischemic stroke patients and clinical outcomes: systematic review of randomized controlled trial study

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ABSTRACT

DLBS1033 is a lumbrokinase earned from extraction of earthworms, *Lumbricus rubellus*. Lumbrokinase has 2 main activities: fibrinolytic and fibrinogenolytic – these activities reduce blood viscosity and platelet aggregation. With all of those properties, DLBS1033 will be a promising agent in patients with ischemic stroke. The objective of this research is to identify the advantage of DLBS1033 in ischemic stroke patients' clinical outcome. We used Pub Med, Cochrane, and Clinical Key as our major database for this systematic review. "DLBS1033", "lumbrokinase", and "stroke" keywords selected to particularize the search. The 2 authors calculated each of the studies using Jadad score. Only certain studies with scores above 3 will be included for further review using PRISMA checklist. There were 27 studies relating to DLBS1033 or lumbrokinase and stroke. Further examination by 2 authors resulted in 23 articles being removed leaving 2 studies. Subjects in all of the said studies are ischemic stroke patients; predominantly male patients. All of the said studies compare DLBS1033 with standard therapy; either utilizing DLBS1033 as an additional therapy or as a separate therapy. Clinical outcomes were measured using NIHSS and BI. Compared to standard therapy, DLBS1033 proved successful in improving clinical outcomes among patients with ischemic stroke. It's also found to be safe with none serious adverse events and significantly has lower bleeding events.

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INTRODUCTION

Stroke can be described as emerging signs of cerebral dysfunction those last more than 24 hours (Aho *et al.*, 1980). Ischemic stroke and hemorrhagic stroke are 2 varieties of stroke, distinguished by their pathomechanism, whether the blood vessel is blocked or burst (Caplan, 2009).

Stroke has claimed the third spot as the major cause of premature death and disability-adjusted life years lost in 2017 (IHME, 2018). Three quarters of stroke patients diagnosed with ischemic stroke. Stroke responsible for almost 6,500,000 deaths (half of them due to ischemic stroke), 113,000,000 disability-adjusted life years lost (0.58 times more often due to ischemic stroke), and 10,300,000 million new cases worldwide in 2013 (Feigin *et al.*, 2013).

No standard therapy has currently been established for ischemic stroke treatment. Several therapies that are frequently used to treat ischemic stroke attack including thrombolytic therapy, antiplatelet agents, anticoagulants and neuroprotective agents (Adams *et al.*, 2007). Some

thrombolytic agents like urokinase (uPA), streptokinase (SK) and tissue urokinase (t-PA) are all typically used to dissolve clots in ischemic stroke. However they're not specific to fibrin and have severe side effects like heavy blood loss (Vernooij, 2009; Delaney *et al.*, 2007). Further, medication with rtPA features a limitation of time. The aforementioned medication should be used less than 3 hours after stroke (Caplan, 2009). Additionally, there are emerging resistance to therapy with the foremost established antiplatelets, aspirin, and clopidogrel (Musallam *et al.*, 2011; Cuisset and Cayla, 2010; Wang *et al.*, 2006).

DLBS1033 is a lumbrokinase earned from extraction of earthworms, *Lumbricus rubellus (Trisina et al., 2011)*. For thousands of years, earthworms have widely been utilized in Indonesia, China, Japan, and therefore the Far East to treat various chronic diseases (Willem & Minne, cited in Simangunsong *et al*., 2016). In 1991, Japanese researchers were the first to use the word 'lumbrokinase' that refers to a cluster of serine protease enzyme in earthworms. Lumbrokinase has 2 main activities: fibrinolytic and fibrinogenolytic – these activities reduce blood viscosity and platelet aggregation (Mihara *et al.*, 1991).

Unlike other thrombolytic agents, such as urokinase (uPA), streptokinase (SK), and tissue plaminogen activator (t-PA); lumbrokinase is extremely specific to fibrin as a substrate and doesn't cause excessive bleeding (Hrženjak *et al.*, 1998). Lumbrokinase has both antithrombotic and thrombolytic activities; thus, unlike the anticoagulants, lumbrokinase suppresses new clots formation and breaks up clots that have already been formed (Trisina *et al.*, 2011; Kurnia and Tjandrawinata, 2011). Lumbrokinase has not shown any adverse effects on the functions of the systema nervosum, systema respiratorium, cardiovascular vessels, or the liver and kidney (16, 17). DLBS1033 has been proven through its toxicological studies in animal (Sukandar *et al.*, 2014) and safety studies in human (Ortiz and Sacco, 2014; Yunaidi *et al.*, 2011). With all of those properties, lumbrokinase will be a promising agent in patients with ischemic stroke.

MATERIALS AND METHODS

We used Pub Med, Cochrane, and Clinical Key as our major database for this systematic review. "DLBS1033", "lumbrokinase", and "stroke" keywords selected to particularize the search.

The selected studies must have these subsequent standards: (i) the study was published in the past 10 years, (ii) full text available in English, (iii) justify the advantage of DLBS1033 as add on therapy in standard therapy of ischemic stroke. Studies other than randomized controlled trial (RCT) won't be reviewed any further.

The 2 authors calculated each of the studies using Jadad score. There are 5 components in Jadad score with score of 5 as the maximum grade. One point is going to be added for each component the study met (Berger and Alperson, 2009) . Only certain studies with scores above 3 will be included for further review using PRISMA checklist. Twenty seven items of PRISMA checklist are used to evaluate systematic review (Liberati *et al.*, 2009).

RESULTS AND DISCUSSION

As shown in Figure 1, there were 27 studies relating to DLBS1033 or lumbrokinase and stroke. After discounting 2 duplicates, there were 25 studies. Further examination by 2 authors resulted in 23 articles being removed leaving 2 studies. Both of those studies were available in full-text articles.

Jadad score was utilized in this systematic review to evaluate the standard of every study. All of the studies graded with score of 3 as shown in Table 1.

Table 2 showing the summary of included studies. Ischemic stroke patients were the subjects and DLBS1033 or lumbrokinase were compared with standard therapy for stroke in all studies. National Institutes of Health Stroke Scale (NIHSS) were used to evaluate clinical outcomes in study by Cao *et al.* (2013). Study by Setyopranoto *et al.* (2016) used Barthel Index (BI) to measure clinical outcomes.

Table 3 summarized the conclusion of every study. DLBS1033 improves patients' clinical outcome. DLBS1033 was considered to be safe for patients with ischemic stroke.

Measurement

NIHSS is disability assessment tool focused on neurological impairment utilized in RCT by Cao *et al.* (2013). NIHSS contains 15-item impairment scale and each scale graded on an ordinal scale (Kwah and Diong, 2014). Normal is described as 0; therefore, the bigger the score, the more severe the neurological impairment (the maximum score is 42) (Ortiz and Sacco, 2014).

Study by Setyopranoto *et al.* (2016) was using BI. BI consists of 10 item-scale (Mahoney and Barthel, 1965). The sum total score ranging from 0 to 100; zero considered as the most severe dependency (Quinn *et al.*, 2011). Scoring on the BI can be classified into: patient able to live independently, dependent (either minimally, partially, or totally), and total dependence (Shinar *et al.*, 1988).

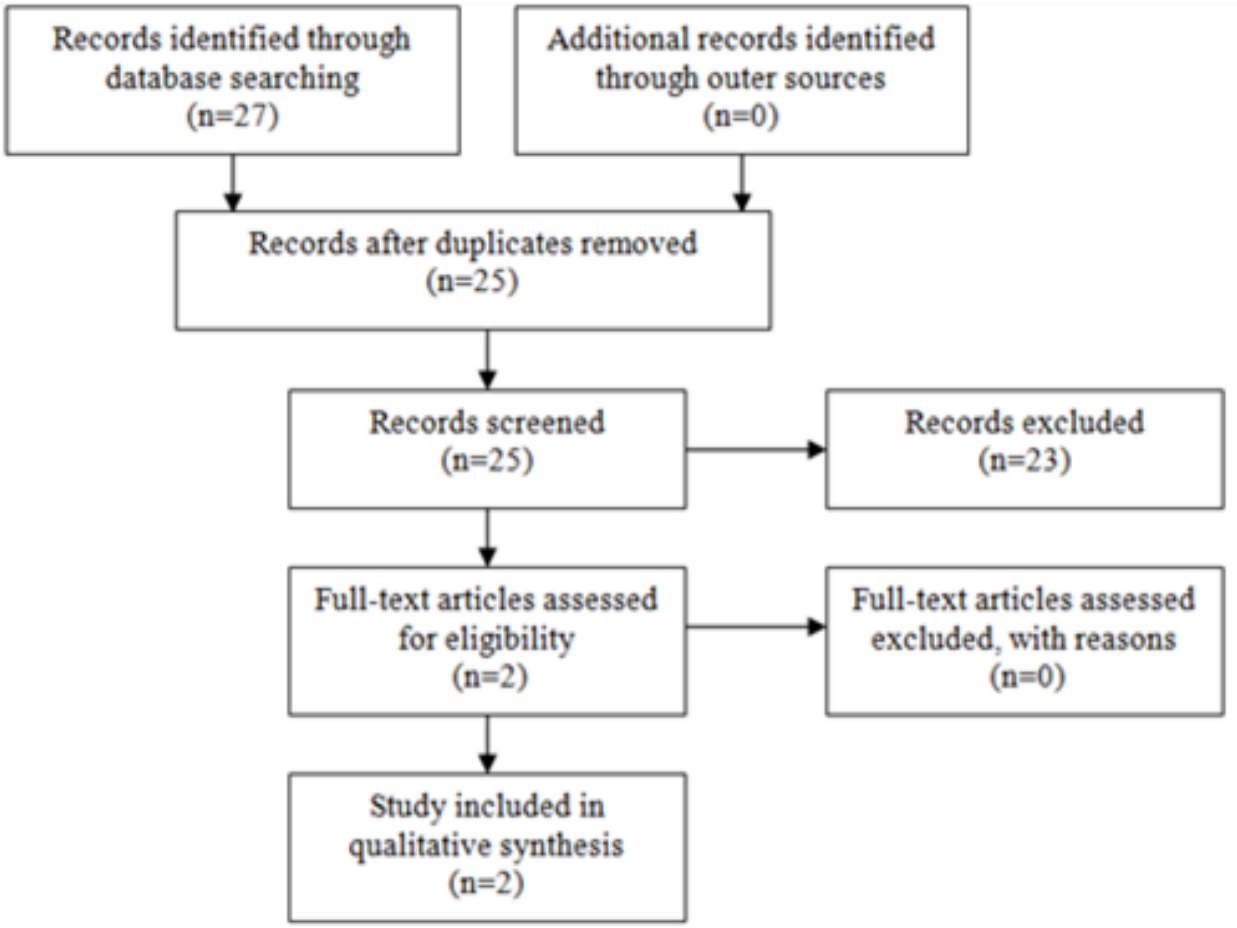

Figure 1: Flow diagram of literature search

Table 1: Evaluation of the Studies by Using Jadad Score

Author (Year)	Was the study described as randomized?	Was the method used to generate the randomization described and appropriate?	Was the study described as double blind?	Was the method of double blinding described any appropriate?	Was there a description of withdrawal and dropout?	Total score
Cao *et al.* (2013)	Yes	Yes	No	No	Yes	3
Setyopranoto *et al.* (2016)	Yes	Yes	No	No	Yes	3

Table 2: Resume of the Selected Studies

Author (Year)	Diagnosis	Intervention	Control	Subject Characteristics	Length of Treatment	Clinical Outcome Measure
Cao *et al.* (2013)	Ischemic stroke	Group 1: Standard stroke treatment + lumbrokinase 600,000 units t.i.d, 30 minutes before meals	Group 2: Standard stroke treatment + placebo t.i.d	N: 310 subjects 217 male, 93 female Group 1: 66.61 ± 8.87 y Group 2: 67.89 ± 9.88 y	12 months	NIHSS
Setyopranoto *et al.* (2016)	Ischemic stroke	Group 1: DLBS1033 490 mg t.i.d	Group 2: Aspirin 80 mg/day Group 3: Clopidogrel 70mg/day	N: 126 subjects 91 male, 35 female	90 days	BI

Table 3: Conclusion of the Selected Studies

Author (Year)	Results
Cao *et al.* (2013)	The treatment group showed favorable outcomes in NIHSS scores
Setyopranoto *et al.* (2016)	DLBS1033 treatment showed higher BI scores improvement. The enhancement of BI was found similar between groups

DLBS1033 and clinical outcomes

Among Jiangsu Province patients, there was statistically significant reduction of NIHSS scores between the lumbrokinase group and also the control group after 1 year of therapy. The NIHSS scores at the baseline and after a half year don't have any significant differences (p: 0.369 and p: 0.178). However, after 1 year the NIHSS scores in both groups were reduced to a greater number. NIHSS scores within the lumbrokinase group showed a meaningful reduction after 1 year compared to the control group (2.35±2.16 vs 3.62±3.53) (p < 0.001) (Cao *et al.*, 2013).

Mean BI scores among ischemic stroke patients within the DLBS1033 group showed the very best improvement in BI score from baseline to day 90, with the size of improvement of 23.09±19.16 from baseline, but it was not significantly different (p=0.098) with that of aspirin (15.12±15.71) or clopidogrel (17.98±19.03). Treatment with DLBS1033 until the end of therapy appeared to be effectively comparable in achieving BI ≥85 compared to aspirin(odds ratio [OR]=0.38; 95% confidence interval [CI], 0.09-1.60; p=0.189). That was also the case with DLBS1033 as compared with clopidogrel (OR= 1.77; 95% CI, 0.61-5.14; p=0.291) (Setyopranoto *et al.*, 2016).

Safety

A study by Cao *et al.* (2013) reported cerebrovascular injuries in 5.93 percent patients: 2 transient ischemic attack, 4 cerebral infarctions, and 1 bleeding within the control group at the 12-month follow up. There was 1 additional event of organ ischemia event within the control group. There were 1.04 percent cerebrovascular incidents inside the lumbrokinase group (1 transient ischemic attack and 1 cerebral infarction), 1 cardiovascular event, and 1 lower gastrointestinal bleeding. Disparities in total vascular and cerebrovascular events among 2 groups were statistically significant (p: 0.046 and p: 0.016). Adverse events were dizziness, nauseating, and vomiting reported from five subjects in

lumbrokinase group and seven subjects in control group. Setyopranoto *et al.* (2016) found neither significantly bleeding events nor adverse events.

CONCLUSIONS

Compared to standard therapy, DLBS1033 turned out successful in improving clinical outcomes among patients with ischemic stroke. It's also found to be safe with none serious adverse events and significantly has lower bleeding events.

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Conflict of Interests

Nothing to declare.

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