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CORRESPONDENCE

Effectiveness of dopaminergic drugs on post stroke recovery: Challenges and new insights

"Are dopaminergic drugs effective for improving stroke patients' functional recovery?" remains an unanswered question. Therefore, depending on personal clinical experience, some clinicians prescribe dopaminergic drugs to stroke patients, whereas other clinicians do not. Occasionally, clinicians in favor of the use of dopaminergic drugs and those against it criticize each other. Notably, "by using ineffective drugs, patients are at an unnecessary risk of several side effects of drugs, such as serotonin syndrome, gastrointestinal trouble, drowsiness, orthostatic hypotension, and sleep disturbance, and patients' economic burden is increased" and "by not using dopaminergic drugs, the opportunity for better motor recovery after stroke is deprived."

Dopamine is a key neurotransmitter for motor learning and acquisition of motor skills, which contributes to motor recovery after stroke. It has been suggested that dopaminergic drugs might improve motor recovery after stroke by enhancing attention and arousal in conditioned learning and up-regulating glutaminergic transmission, which increases synaptic efficacy.[1,2]

The PubMed database was searched for articles that were published until August 31, 2020. The following key phrases were employed to make the search explicit: [stroke AND (dopaminergic drug OR levodopa); and (function OR recovery)]. The inclusion criteria for the selection of articles encompassed studies that: 1) displayed effectiveness of dopamine agonists on motor recovery after stroke was evaluated; 2) were randomized controlled trial. Review articles were excluded from this study. The primary perusal of literature yielded 1,161 potentially relevant papers. After examining the titles and abstracts of the articles and assessing them for eligibility based on the full-text articles, eight reported works were finally included in this study. However, the results of the selected studies were inconsistent.[1,2] In four of the studies, no improvement in motor function was observed. While in the remaining four studies, a positive outcome was observed (Table 1). These inconsistent results have contributed to the increased confusion with respect to the usage of dopaminergic drugs on stroke patients.

However, these previous studies had some limitations. First, all of the eight previous studies recruited patients without adjusting for stroke lesions and corticospinal tract states (Table 1). Stroke lesions are important factors for determining the prognosis of motor function.[3] Although motor functions are similar in the early stage after stroke, patients whose lesions are in the cerebral cortex show better motor recovery than those with lesions in the subcortex.[3] Moreover, among subcortical areas, patients whose lesions are in the posterior limb show a particularly poor motor outcome.[3] Additionally, the corticospinal tract is the most important neural tract in humans.[3] Its preservation after stroke is an essential factor for excellent motor recovery.[3] Therefore, for evaluating the effectiveness of treatments for improving motor recovery after stroke, adjusting for these important factors, such as stroke lesions and corticospinal tract, is necessary.

Second, previous studies have displayed significant heterogeneity with respect to the periods after stroke onset in the studied patients (Table 1). Motor recovery after stroke occurs rapidly during the first month after stroke onset and then slows down in the following 1–3 months.[4] Between 3 and 6 months after stroke onset, motor recovery slows further down to levels that are hardly noticeable.[5] From 6 months after the onset, the motor recovery slope reaches a plateau.[5] Therefore, a heterogeneous and wide range of periods after stroke onset of included patients hinders the accurate evaluation of the effect of dopaminergic drugs on motor recovery. For example, if the patients in the early stage after stroke onset are more included in the placebo group than in the group in which dopaminergic drugs were applied, the effect of dopaminergic drugs could be underestimated.

Third, we believe that motor function in stroke patients cannot be fully evaluated by the tools used in previous studies (Table 1). Many measurements used in previous studies, such as the Barthel index, Fugl–Meyer assessment, gait independency, and grip power, cannot reflect the presence or degree of abulia or apraxia. However, abulia or apraxia could affect motor function in stroke patients, and it seemed that the effect of dopaminergic drugs on these symptoms was neglected in the previous studies.[5]

Table 1: Summary of the previous studies on the effectiveness of dopaminergic drugs on motor recovery after stroke

First author (year), design	Period after stroke	Medication (dose, number of patients)	Measured outcome	Response
[1]Ford (2019), RCT	5–41 days after ischemic or hemorrhagic stroke	Co-careldopa (62.5 or 125 mg, n = 308) vs. placebo (n = 285)	Ability to walk independently	-
[2]Lokk (2011), RCT	15–180 days after ischemic stroke	Methyphenidate (20 mg) + levodopa (125 mg, n = 25) vs. methyphenidate (20 mg, n = 25) vs. levodepa (125 mg, n = 25) vs. placebo (n = 25)	BI, FMA, and NIHSS	BI and NIHSS: +, drug: BI –25~30.5↑, NIHSS – 2.6~3.6↓ vs. placebo: BI – 16.5↑, NIHSS – 1.9Symbol FMA: -
[3]Cramer (2009), RCT	1–12 months after ischemic or hemorrhagic stroke	Ropinirole (0.25 to 4 mg, n = 17) vs. placebo (n = 16)	Gait velocity	-
[4]Acler (2009), RCT	10–48 months after ischemic stroke	Levodopa (100 mg, n = 6) vs. placebo (n = 6)	Walking speed and NPT	+, drug: 10MWT – 8s↓, NPT – 20↓ vs. placebo: 10MWT – no change, NPT – 3↓
[5]Rosser (2008), RCT	≥1 year after ischemic or hemorrhagic stroke	Levodopa (300 mg) + carbidopa (75 mg) (n = 9) vs. placebo (n = 9)	Procedural motor learning reaction times	Procedural motor learning +: but no numerical data reaction times -
[6]Restemeyer (2007), RCT	>6 month after ischemic or hemorrhagic stroke	Levodopa (100 mg, n = 5) vs. placebo (n = 5)	Nine–Hole–Peg test, grip strength, and Action Research Arm test	-
[7]Sonde (2007), RCT	5–10 days after ischemic or hemorrhagic stroke	Amphetamine (20 mg, n = 7) vs. levodopa (100 mg, n = 4) vs. amphetamine 10 mg + levodopa 50 mg (n = 7) vs. placebo (n = 7)	FMA and BI	-
[8]Scheidtmann (2001), RCT	3 weeks to 6 months after ischemic or hemorrhagic stroke	Levodopa (100 mg, n = 26) vs. placebo (n = 25)	RMA	+, levodopa: RMA – 8.2↑ vs. placebo: RMA – 5.7↑

Abbreviations: RCT, randomized controlled trial; BI, Barthel index; FMA, Fugl–Meyer Assessment; NIHSS, National Institutes of Health Stroke Scale; 10MWT, 10 meter waking test; NPT, Nine Pegboard Test RMA, Rivermead Motor Assessment

[1]Ford GA, Bhakta BB, Cozens A, *et al*. Safety and efficacy of co-careldopa as an add-on therapy for occupational and physical therapy in patients after stroke (DARS): a randomized, double-blind, placebo-controlled trial. *Lancet Neurol* 2019;18:530-8.

[2]Lokk J, Roghani RS, Delbari A. Effect of methylphenidate and/or levodopa coupled with physiotherapy on functional and motor recovery after stroke: a randomized, double-blind, placebo-controlled trial. *Acta Neurol Scand* 2011; 123: 266-73.

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Fourth, the drug dosages used in the previous studies were heterogeneous, therefore the optimal dosages of dopaminergic drugs cannot be determined. Lastly, except for Ford *et al*.'s study[2], the sample sizes of the published studies were relatively small.

In summary, we indicate some limitations in the previous studies: 1. Stroke and corticospinal tract states were not controlled; 2. The periods after stroke onset in the included patients were not homogenous; 3. The improvement of abulia or apraxia by medication was not considered; 4. The optimal dosages of dopaminergic drugs are unclear; 5. The sample sizes in most of the previous studies were small. Due to these limitations in the previous studies, the effect of dopaminergic drugs on motor recovery after stroke does not seem to have been properly evaluated. Inconsistency in the results of previous studies could be, at least in part, attributed to these limitations. To eliminate controversies regarding the use of dopaminergic drugs on stroke patients, researchers must analyze their results by adjusting the stroke lesion and corticospinal tract state and include patients whose periods after stroke onset are similar. The effect of dopaminergic drugs on abulia or apraxia should also be evaluated. Additionally, efforts to find the optimal dose of dopaminergic drugs would be needed, and further studies involving large numbers of subjects are necessary.

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DISCLOSURE

Conflicts of interest: None

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