Synergic Effect of Robot-Assisted Rehabilitation and Antispasticity Therapy

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Stroke and spinal cord injury are neurological disorders that cause disability and exert tremendous social and economic effects. Robot-assisted training (RAT), which may reduce spasticity, is widely applied in neurorehabilitation. The combined effects of RAT and antispasticity therapies, such as botulinum toxin A injection therapy, on functional recovery remain unclear. Combined therapy improves functional recovery in the lower limbs but does not reduce spasticity in the upper or lower limbs.

Keywords: stroke ; spinal cord injury ; robotic-assisted therapy ; antispasticity therapy

1. Introduction

Stroke and spinal cord injury (SCI) are common diagnoses among patients receiving inpatient rehabilitation and often limit such patients' abilities to perform activities of daily living. Most patients with stroke or SCI experience functional impairment, spasticity, and motor clumsiness [1], and spasticity and functional impairment are the primary reason for rehabilitative intervention in the chronic stages of recovery [2][3][4]. A major line of inquiry in rehabilitation sciences is the development of therapies optimized for managing spasticity and functional impairment in such patients.

Spasticity is a motor disorder that manifests as an increase in tonic stretch reflexes caused by hyperexcitability of the stretch reflex in patients with upper motor neuron disorders, such as stroke and SCI [5]. Spasticity occurs in 4–27% and 17–46% of patients with stroke within the first month and first 3 months after stroke, respectively, and in 70% of patients with SCI [6][7][8][9]. Spasticity limits the performance of daily activities, social participation, and quality of life [10]. Controlling spasticity is essential to alleviating its resulting functional impacts [11][12]. Therefore, a major line of inquiry in rehabilitation sciences is the development of therapies optimized for managing spasticity.

In recent 10 years, robot-assisted training (RAT) has been applied for improving impaired motor function in patients with neurological disorders. RAT is superior to conventional therapies for neurorehabilitation in both the upper [13][14] and lower limbs [15] because it integrates high-intensity, repetitive, and task-specific training. It can also measure a patient's performance with high reliability and accuracy [16]. However, despite the evident utility of RAT, whether a combination of RAT and other therapies can yield a synergic effect remains unclear.

2. Risk-of-Bias Assessment

The risk of bias in the included studies was assessed using the modified Jadad scale (**Table 1**). The scores of the included studies ranged from 3 to 5.5, indicating a considerable risk of bias. The methods of randomization and blinding were the major causes of the high risk of bias.

3. Features of Included Studies

Table 1 summarizes the characteristics of the included studies. All the eligible studies were RCTs published between 2015 and 2019. Four of the studies enrolled patients with stroke, and one enrolled patients with SCI. Two of the studies (Gandolfi et al., 2019 [17] and Pennati et al., 2015 [18]), both of which enrolled patients with stroke, assessed motor function of the upper limbs. The other three studies, among which two (Picelli et al., 2016 [19] and Erbil et al., 2018 [20]) enrolled patients with stroke and one (Duffell et al., 2015 [21]) enrolled patients with SCI, assessed the motor function of the lower limbs. Each of the included studies enrolled 15 to 48 patients, and 29% to 40% of each sample consisted of female patients. The mean ages of the patients ranged from 46.5 to 65.1 years. The mean intervals between disease onset and enrollment ranged from 6 months to 20 years. The number of RAT sessions ranged from 10 to 15, and the intervention durations ranged from 5 days to 5 weeks. The mean follow-up intervals ranged from 0 days (immediately after treatment) to 12 weeks.

Table 1. Demographic data of patients in included studies.

Author, Year	Disease	Limbs of Evaluation	Total No. of Patients (F/M)	Group	No. of Patients (F/M)	Mean Age, Year (SD)	Time since Injury (SD)
Gandolfi et al., 2019 [17]	**Stroke**	**UL**	**32 (10/22)**	**Control**	**16 (6/10)**	**59.13 (14.97)**	**5.1 yr (2.2 yr)**
				Intervention	**16 (4/12)**	**59.31 (14.40)**	**6.0 yr (3.1 yr)**
Pennati et al., 2015 [18]	**Stroke**	**UL**	**15 (6/9)**	**Control**	**8 (NA)**	**NA**	**>6 mo, (10 mo to 20 yr)**
				Intervention	**7 (NA)**	**NA**	**>6 mo, (10 mo to 20 yr)**
Picelli et al., 2016 [19]	**Stroke**	**LL**	**22 (6/16)**	**Control**	**11 (4/7)**	**65.1 (3.4)**	**6.1 yr (3.8 yr)**
				Intervention	**11 (2/9)**	**62.4 (9.5)**	**6.2 yr (4.2 yr)**
Erbil et al., 2018 [20]	**Stroke**	**LL**	**43 (16/27)**	**Control**	**14 (3/11)**	**48.7 (10.4)**	**25.9 mo (24.6 mo)**
				Intervention	**29 (13/16)**	**50.1 (11.8)**	**39 mo (34.3 mo)**
Duffell et al., 2015 [21]	**SCI**	**LL**	**48 (14/34)**	**Control**	**26 (7/19)**	**46.6 (12.6)**	**9.3 yr (8.9 yr)**
				Intervention	**22 (7/15)**	**46.5 (11.9)**	**10.2 yr (10.47 yr)**

4. Intervention Protocols

The intervention protocols employed in the included studies varied widely. Two of the studies involved upper limb interventions: that by Gandolfi et al., who recruited 32 patients and compared BoNT + RAT with BoNT + physical therapy, and that by Pennati et al., who recruited 15 patients and compared BoNT + RAT with RAT alone. The studies by Picelli et al., who recruited 22 patients and compared BoNT + robot-assisted gait training (RAGT) with BoNT alone; Erbil et al., who recruited 43 patients and compared BoNT + RAGT + PT with BoNT + PT; and Duffell et al., who recruited 48 patients and compared RAGT + oral tizanidine with RAGT alone, all focused on lower limb interventions.

5. Primary Outcome: Functional Recovery

In the two studies, the evaluated functional improvement in the upper limbs, the FMA, MRC, and B&B were used to measure the outcomes. Pennati et al. reported that the FMA and B&B scores of the patients who received RAT alone improved significantly more than did those of the patients who received combined therapy (BoNT + RAT), whereas Gandolfi et al. reported no significant differences in FMA and MRC score improvements between the patients who received BoNT + PT and those who received BoNT + RAT. In summary, the included studies yielded conflicting conclusions regarding the effect of combination therapy on functional recovery in the upper limbs.

In the three studies that assessed functional improvement in the lower limbs, the outcomes were measured using the 6MWT, BBS, TUG, RVGA, and 10MWT. Picelli et al. reported that the 6MWT results of the patients who received combined therapy (BoNT + RAT) improved more than those of the patients who received BoNT alone. Erbil et al. reported that the BBS, TUG, and RVGA scores of the patients who received combined therapy (BoNT + PT + RAGT) improved more than those of the patients who received BoNT + PT. Duffell et al. reported that the 10MWT results of the patients who received RAGT + oral tizanidine improved discernably (according to the minimal important difference), whereas those of the patients who received RAGT alone did not. In summary, combined therapies are more effective in promoting functional recovery in the lower limbs.

6. Secondary Outcome: Spasticity

The secondary outcome was spasticity reduction. To determine whether the patients who received combined therapy experienced greater reductions in spasticity than those who received other interventions, researchers analyzed the spasticity assessment results in the included reports. Four of the studies used the MAS, two used the Tardieu Scale, and one (Duffell et al.) did not report spasticity. The two studies that assessed spasticity by using the MAS focused on the upper limbs. Pennati et al. reported that the MAS scores of the patients who received combined therapy (BoNT + RAT) decreased more than those of the controls; however, Gandolfi et al. did not report similar results.

Two of the studies that focused on the lower limbs (Picelli et al. and Erbil et al.) adopted the MAS and Tardieu Scale to evaluate spasticity. In these two studies, the scores of the MAS or Tardieu Scales of the patients in the combined therapy groups did not decrease more than those of the controls.

7. Power Analysis and Effect Size

Only two of the included studies reported effect sizes: that by Gandolfi et al., in which the effect size ranged from −0.02 to 0.49, and that by Picelli et al., in which the effect size ranged from 0.07 to 0.47. However, the methods employed for effect size estimation in these studies were not delineated. These studies also performed power analysis, which revealed that their sample sizes were sufficient for avoiding type II errors. Because the other three studies did not report their effect sizes and did not perform power analysis, the effectiveness of the interventions evaluated therein could not be adequately inferred, and their results could have been a result of inadequate sample size.

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