ORIGINAL REPORT

EFFECTS OF ALTERNATING BILATERAL TRAINING BETWEEN NON-PARETIC AND PARETIC UPPER LIMBS IN PATIENTS WITH HEMIPARETIC STROKE: A PILOT RANDOMIZED CONTROLLED TRIAL

Masashi KUMAGAI, OT, PhD[1,2], Shintaro UEHARA, PT, PhD[3], Taichi KURAYAMA, PT, PhD[4], Shin KITAMURA, OT, MS[1,3,5], Sachiko SAKATA, OT, MS[1], Kunitsugu KONDO, MD, PhD[1], Eiji SHIMIZU, MD, PhD[2], Naoki YOSHINAGA, RN, PhD[6] and Yohei OTAKA, MD, PhD[1,7]

From the [1]Department of Rehabilitation Medicine, Tokyo Bay Rehabilitation Hospital, Chiba, [2]Department of Cognitive Behavioral Physiology, Chiba University Graduate School of Medicine, Chiba, [3]Faculty of Rehabilitation, School of Health Sciences, Fujita Health University, Aichi, [4]Faculty of Health Sciences, Uekusa Gakuen University, Chiba, [5]Department of Occupational Therapy, Tokyo Metropolitan University Graduate School of Human Health Sciences, Tokyo, [6]School of Nursing, Faculty of Medicine, University of Miyazaki, Miyazaki and [7]Department of Rehabilitation Medicine I, Fujita Health University School of Medicine, Aichi, Japan

Objective: To examine whether alternating training with both the non-paretic and paretic sides (alternating bilateral training), expecting trial-to-trial inter-limb transfer of training effects from the non-paretic to the paretic side, improves upper-limb motor performance in post-stroke patients, compared with unilateral training involving only the paretic side.
Design: An assessor-blinded pilot randomized controlled trial.
Subjects: Twenty-four right-handed post-stroke patients with hemiparesis.
Methods: Participants were randomly allocated to either an alternating bilateral training group or a unilateral training group (*n* = 12/group). Participants underwent dexterity training of the paretic arm using the Nine-Hole Peg Test, completing 10 trials/day for 7 consecutive days. The alternating bilateral training group additionally performed alternating trials with the non-paretic limb. Performance change, assessed 1 day and 1 week after the 7-day training period, was compared between groups.
Results: Although the improvement was comparable in both groups at both post-training time-points, a sub-analysis in which those with left hemiparesis and those with right hemiparesis were analyzed separately revealed potential benefits of the alternating bilateral training, specifically for those with left hemiparesis.
Conclusion: Alternating bilateral training may augment training effects and improve upper-limb motor function in patients with left hemiparesis.

Key words: alternating bilateral training; cerebrovascular disorders; dexterity; hemiparesis; inter-limb transfer; upper extremity.

LAY ABSTRACT

Post-stroke patients often experience long-term impairments affecting dexterity and motor control of the paretic upper limb. Recent studies have suggested that a unique training method, based on the inter-limb transfer phenomenon, expecting transfer of the training effect of the trained to the contralateral limb, has the potential to improve the performance of the paretic side. However, this traditional model focuses on training only with the non-paretic side, and thus cannot be directly applied to clinical settings. This study developed and evaluated the effect of a new clinically relevant strategy in which post-stroke patients underwent alternating training of the upper limbs of the non-paretic and paretic sides. Although the training effect was comparable with that of the unilateral training involving only the paretic side, a sub-analysis revealed a potential benefit of the alternating training specifically for left hemiparetic patients. The proposed training strategy could help post-stroke patients improve upper-limb motor function.

Correspondence address: Yohei Otaka, 1-98 Dengakugakubo, Kutsu-kake, Toyoake, Aichi 470-1192, Japan. E-mail: otaka119@mac.com

Paresis of the upper extremity is a frequent impairment following acute stroke, which occurs in up to three-quarters of patients (1). Although partial improvement of motor dysfunction is experienced during the recovery phase, many patients experience long-term impairments affecting dexterity and motor control of the paretic upper extremity (2–4). Among the many training methods employed to facilitate the recovery of post-stroke patients, only a few have been shown to be efficacious in improving the dexterity of the paretic upper limb (5, 6). Moreover, a systematic review concluded that existing techniques were not effective, especially for improving motor function in a paretic hand (7).

Recently, it has been reported that a unique training method, based on the phenomenon of inter-limb

transfer, has the potential to improve task performance on the paretic side in post-stroke patients (8–13). Inter-limb transfer is a phenomenon in which a training effect is transferred from a trained limb to an untrained limb; this effect has been known for more than a century (14), and many studies on this effect have involved healthy individuals (14–19). However, only a few studies have investigated the inter-limb transfer effect to improve the dexterity performance of the paretic upper extremity in post-stroke patients (8, 9). Furthermore, most of the previous applications of inter-limb transfer in post-stroke patients with hemiparesis have involved experimental protocols, in which only the non-paretic side is trained based on the traditional inter-limb transfer model (20), with the expectation that the training effect would transfer to the paretic side (8–12). In actual clinical settings, however, training of the paretic side has been considered an essential component of rehabilitation according to accumulating evidence supporting the importance of use-dependent and repetitive training effects (5, 21). Therefore, the training protocol based on the traditional inter-limb transfer model cannot be directly applied in the clinical setting, especially when targeting individuals with mild to moderate hemiparesis who have remaining motor capacity to perform training with the paretic limb.

The current study developed and evaluated the effect of a new training strategy, which would likely be suitable for a clinical setting, in which patients repeatedly underwent alternating training of the upper limbs between the non-paretic and paretic sides (alternating bilateral training; ABT). This pilot randomized controlled trial aimed to examine the effect of ABT and its effect sizes on the dexterity performance of the affected upper limb in post-stroke patients with mild to moderate hemiparesis. The hypothesis was that ABT, probably having a mixture of effects of both trial-to-trial inter-limb transfer from the non-paretic limb and of training with the paretic limb *per se*, would lead to better improvement in the dexterity performance of the paretic limb compared with training with the paretic limb alone.

MATERIAL AND METHODS

Study design
The study was an assessor-blinded randomized controlled trial. The study protocol was approved by the ethics review board of Tokyo Bay Rehabilitation Hospital (approval number: 91-2) and it was registered in the UMIN Clinical Trials Registry (UMIN000013346, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000015576) prior to the recruitment of participants. All participants provided written informed consent prior to their participation, and the study was conducted in accordance with the Declaration of Helsinki 1964, as revised in 2013.

Participants
Patients who were admitted to Tokyo Bay Rehabilitation Hospital for stroke treatment between March 2014 and March 2015 were consecutively enrolled. Among these patients, the 24 who fulfilled the following inclusion/exclusion criteria participated in the study: first-ever stroke, a period of more than 2 months after stroke onset, a score on the knee-mouth test of the Stroke Impairment Assessment Set (22, 23) ranging from 3 to 5, a score on the finger-function test of the Stroke Impairment Assessment Set ranging from 3 to 5, a Nine-Hole Peg Test (NHPT) time ranging from 30 to 60 s for the paretic side, and a difference in the time required to complete the NHPT between the non-paretic and the paretic side exceeding 5 s. The exclusion criteria were as follows: inability to follow 3-step commands, severe pain in the upper extremity, musculoskeletal problems affecting the upper extremity, multiple brain lesions, lesions in the cerebellum, subarachnoid haemorrhage, and central nervous disorders other than stroke. Participants' clinical and demographic information, including age, sex, Edinburgh Handedness Inventory score (24), type of stroke, duration from onset of stroke, side of paresis, and the Fugl-Mayer Assessment Scale score for the upper extremity (25), were obtained.

Training
The participants were asked to train the dexterity of the affected upper limb using the NHPT. The NHPT, which consists of 9 pegs and a pegboard with 9 holes, is used to assess hand and finger dexterity (26). The test has been shown to have high reliability and validity in patients with stroke (27, 28). During the task, the participants were asked to pick up a peg from a container and to place the peg in a hole on the board; this was repeated 1 peg at a time until all 9 holes were filled. Then, the participants were asked to put the pegs back into the container one at a time. They were instructed to perform these processes as quickly and accurately as possible.

The participants performed 10 trials of the NHPT with the paretic limb each day for 7 consecutive days (Fig. 1). Participants assigned to the ABT group performed the NHPT with the paretic limb alternatingly with the non-paretic limb (with the non-paretic side first), whereas those assigned to the unilateral training (UT) group performed only the task with the limb on the paretic side. In other words, the ABT group
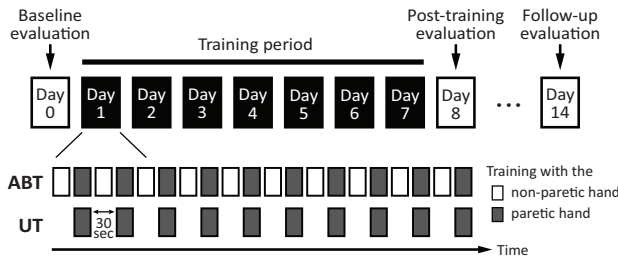
Fig. 1. Training protocols for alternating bilateral training (ABT) and unilateral training (UT).

performed a trial with the non-paretic side prior to each trial with the paretic side, 10 trials for each side, resulting in 20 trials in total, whereas the UT group performed 10 trials with the paretic side only. To control for fatigue effects that could have potentially occurred in the UT group due to repetitive trials involving the paretic side, the participants in the UT group were allowed to take a 30-s break between trials. The time required to complete the transport of all 9 pegs back to the original location was recorded and reported to the participants after each trial to ensure that they maintained their motivation. If a participant dropped a peg, the trial was stopped and restarted from the beginning. The participants performed daily NHPT training after completing their usual daily rehabilitation: 60-min physical and 60-min occupational therapies consisting of trainings for basic movements, walking, activities of daily living (ADL), instrumental ADL, and functional motor training for the upper limb without using NHPT, according to patients' needs and degree of impairments.

Outcomes
Primary outcome measure. The primary outcome was the training effect, which was defined as the amount of change in the time required to complete the NHPT task, 1 day and 1 week after the 7-day training period. The time in seconds required to completely transport all 9 pegs back to the container was used as a proxy measure of task performance. Based on the mean performance of 3 NHPT trials evaluated 1 day before (baseline), 1 day after (post-training), and 1 week after (follow-up) the 7-day training period, the differences in task performance from baseline were calculated for both the paretic and non-paretic sides. At each time-point, the participants performed a block of 3 consecutive NHPT trials, first with the paretic side and then with the non-paretic side.

Secondary outcome measures. The Purdue Pegboard Test (29) and the Box and Block Test (27, 30) were performed with the limb on the paretic side, and were employed as secondary outcome measures to examine the generalizability of any improvements in the NHPT

performance in different dexterity tasks involving different sized and shaped objects.

The Purdue Pegboard Test consists of a rectangular board with 2 sets of 25 holes running vertically. Among the 4 subtests, this study employed 2 tasks involving a single upper limb in which the participants were tasked with putting small metal pegs into holes using the upper limb on the paretic or non-paretic side as rapidly as possible. The number of pegs placed within 30 s was recorded, with a higher score reflecting better dexterity.

The Box and Block Test consists of a box with a partition in the middle and 150 blocks (2.5×2.5 cm). Participants were instructed to grasp 1 block at a time from 1 compartment, transport it over the partition, and release it into the opposite compartment using a single hand. The score was determined based on how many blocks participants could transfer in 60 s, with higher scores indicating better dexterity. The Box and Block Test has been shown to have high test-retest reliability in patients with hemiparetic stroke (27).

For both tasks, the changes in performance from baseline were assessed at 1 and 7 days (post-training and follow-up) after the training period, based on the mean of 3 trials at each time-point.

Sample size
Because there was a lack of knowledge about the effect size of the intervention, a sample size (12/group) was selected based on the minimum sample size needed in a pilot study (31).

Randomization
For allocation of the participants, a person who was not involved in the current study stratified the subjects into the following 2 groups based on the baseline performance on the NHPT: those with times from 30 s to <45 s, and those with times from 45 s to <60 s. Subsequently, the same person randomly assigned the participants to one of the 2 training groups in a blocked manner (block size=4) according to a computer-generated list of random numbers. The allocation procedure was concealed until all allocations were conducted.

Blinding
While the participants and the occupational therapist (MK) supervising the training were aware of the group allocations because of the nature of the interventions, the outcome assessor (SK) was kept blinded to the allocations until the end of the study.

Analysis and statistics
Baseline clinical and demographic characteristics of the participants were compared between the 2 groups. Continuous variables were analyzed using unpaired

t-tests or Mann–Whitney *U* tests. Categorical variables were analyzed using Fisher's exact tests. Analyses of the primary and secondary outcome measures were performed on an intention-to-treat basis. To assess the differences in the training effect (i.e., the change in performance from the baseline) between the 2 groups, Mann–Whitney *U* tests were applied separately for the 1-day post-training and 7-day follow-up time-points for the paretic and non-paretic sides.

Previous studies investigating the inter-limb transfer effects have demonstrated a potential difference in the magnitude of the training effects transferred to the opposite limb, depending on whether the training was performed with the limb on the dominant or non-dominant side (16–18). This led to the assumption that the effect of ABT could differ between participants with right and left hemiparesis in the current study in which all the participants were right-handed. Those with right hemiparesis in the ABT group were expected to gain the transfer effects from the non-dominant left side to the dominant right side, whereas in the participants with left hemiparesis the transfer effects were expected from the dominant right side to the non-dominant left side. To test this possibility, participants were subdivided into groups with right or left hemiparesis, and then the effect of the 7-day training was compared between the ABT and UT groups within each hemiparetic subgroup.

IBM Statistical Package for the Social Sciences (SPSS) Statistics 23 (IBM Corp., USA) was used for all statistical analyses. Any *p*-values <0.05 were considered statistically significant. Effect sizes were reported as the *r* values of the Mann–Whitney *U* tests.

RESULTS

Fig. 2 illustrates the flow chart of the participants' recruitment and progression through the trial. Among the 436 consecutive patients treated for stroke, 24 right-handed participants fulfilled the selection criteria and were randomly assigned to either the ABT ($n=12$) or UT ($n=12$) group. All participants completed the entire study protocol and were included in the final analyses according to the initially assigned groups. The clinical and demographic characteristics of the participants did not differ between the groups (Table I).

Primary outcome measure
Although both the ABT and UT groups exhibited improved performance on the paretic side after the training period (Fig. 3A, Table II), the amount of change was not significantly different between the groups at either
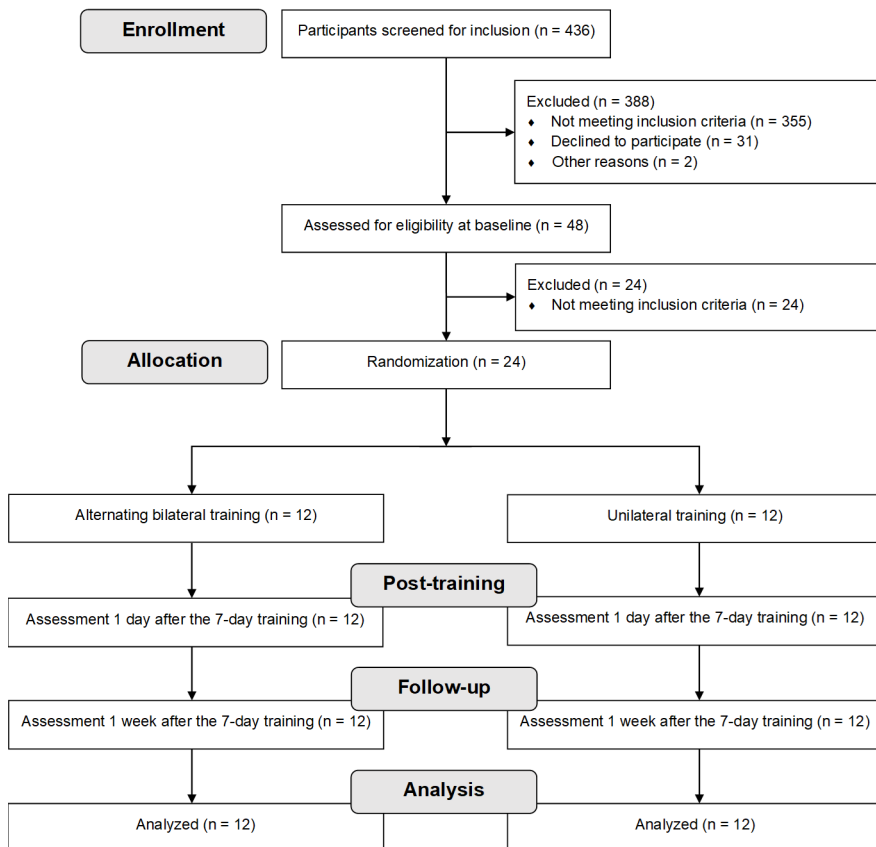

Fig. 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the participants' recruitment and progression through the phases of the trial.

Table I. Participants' characteristics

Characteristics	ABT group	UT group	*p*-value
Age, years, mean (SD)	72.4 (17.6)	70.3 (12.1)	0.739
Sex, female/male, *n* (female %)	9/3 (75)	7/5 (58)	0.667
Handedness, right/left, *n*	12/0	12/0	0.999
Edinburgh Handedness Inventory, %, median (IQR)	100 (13)	100 (10)	0.829
Type of stroke, haemorrhage/infarction, *n*	6/6	7/5	0.999
Duration from onset, days, mean (SD)	97.9 (23.6)	92.5 (24.9)	0.589
Paretic side, right/left, *n*	7/5	6/6	0.999
Fugl-Meyer Assessment for the upper extremity, score, median (IQR)			
Motor function	63.0 (7.0)	62.5 (7.0)	0.977
Sensation	11.0 (2.5)	11.0 (3.0)	0.927
Passive joint motion	23.0 (1.5)	24.0 (3.0)	0.690
Joint pain	24.0 (1.0)	24.0 (2.5)	0.550

ABT: alternating bilateral training; UT: unilateral training; SD: standard deviation; IQR: interquartile range.

Fig. 3. Amount of change in performance on the Nine-Hole Peg Test (NHPT) for the paretic (A) and non-paretic (B) sides at the post-training (1 day after training) and follow-up (7 days after training) time-points. The *light green* and *light blue* boxplots represent the data of the alternating bilateral training (ABT) and unilateral training (UT) groups, respectively. The *horizontal lines* inside the boxplots represent the median values, the *edges* of the boxplots represent the upper and lower quartiles, the *whiskers* show the non-outlier maximum and minimum values, and the *dots* are the outliers. The *horizontal lines* below the boxplots indicate a significant difference between the ABT and UT groups ($p < 0.05$).

the post-training ($U=68.0, Z=-0.23, p=0.843, r=0.05$) or follow-up time-points ($U=70.0, Z=-0.12, p=0.932, r=0.02$). Importantly, the task performance on the non-paretic side showed significantly greater improvement in the ABT than in the UT group at the post-training ($U=28.0, Z=-2.54, p=0.010, r=0.52$) and follow-up time-points ($U=24.5, Z=-2.74, p=0.005, r=0.56$, Fig. 3B). These results seemingly indicate that additional training of the limb on the non-paretic side showed the effect on the same side; however, it did not provide further gains in the training effect on the paretic side.

Regardless of these overall trends, a sub-analysis conducted after separating the participants with right and left hemiparesis revealed a different tendency of the training effects (Table SI). In the participants with right hemiparesis (left panel in Fig. 4A), the change in the performance on the paretic right side did not significantly differ between the groups at either the post-training ($U=32.0, Z=1.57, p=0.138, r=0.44$) or follow-up ($U=28.0, Z=1.00, p=0.366, r=0.28$) time-points. In contrast, the improvement in performance
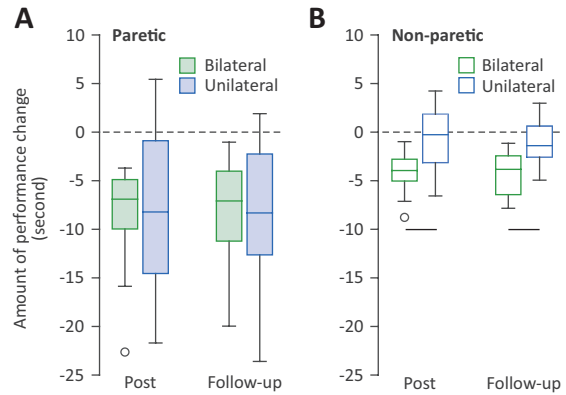
on the paretic left side in those with left hemiparesis was significantly greater in the ABT group than in the UT group, specifically at the post-training time-point ($U=3.0, Z=-2.19, p=0.030, r=0.66$); this effect may mainly be attributed to the marginal improvement observed in the UT group, even after the 7-day training period (right panel in Fig. 4A). In support of the effect that the training of the non-paretic side had on the performance on that same side (left and right panels in Fig. 4B), the performance on the non-paretic side in the ABT group showed significantly greater improvements than that in the UT group, at least at the follow-up time-point ($U=6.5, Z=-2.07, p=0.035, r=0.57$) in those with right hemiparesis, as well as at the post-training time-point ($U=0.5, Z=-2.65, p=0.004, r=0.80$) in those with left hemiparesis. The results of

Table II. Primary and secondary outcomes of the paretic and non-paretic sides

Outcome variables	Groups	Baseline	Post-training (1 day after training)	Follow-up (7 days after training)
Paretic side				
Nine-Hole Peg Test, s	ABT	43.7 (8.5)	34.9 (6.9)	35.8 (7.5)
	UT	43.8 (9.3)	35.9 (7.2)	35.7 (5.6)
Purdue Pegboard Test, number of pegs	ABT	6.3 (2.0)	7.1 (1.9)	7.1 (2.3)
	UT	5.7 (1.9)	6.2 (1.8)	6.3 (1.2)
Box and Block Test, number of blocks	ABT	36.0 (8.9)	39.7 (8.5)	40.1 (7.7)
	UT	32.5 (9.7)	35.6 (10.3)	39.0 (9.4)
Non-paretic side				
Nine-Hole Peg Test, s	ABT	25.3 (4.3)	21.1 (4.1)*	20.9 (3.3)*
	UT	27.0 (5.6)	26.3 (5.4)	25.9 (5.9)
Purdue Pegboard Test, number of pegs	ABT	10.4 (3.3)	11.1 (2.8)	11.4 (3.0)
	UT	9.8 (2.1)	10.0 (2.5)	10.7 (2.3)
Box and Block Test, number of blocks	ABT	52.6 (9.6)	57.4 (10.1)	56.9 (8.4)*
	UT	47.5 (15.2)	49.0 (15.1)	54.5 (16.9)

Values are presented as mean (standard deviation).
ABT: alternating bilateral training; UT: unilateral training.
*Significant difference in the amount of performance change between the ABT and UT groups based on the Mann–Whitney *U* tests ($p < 0.05$).
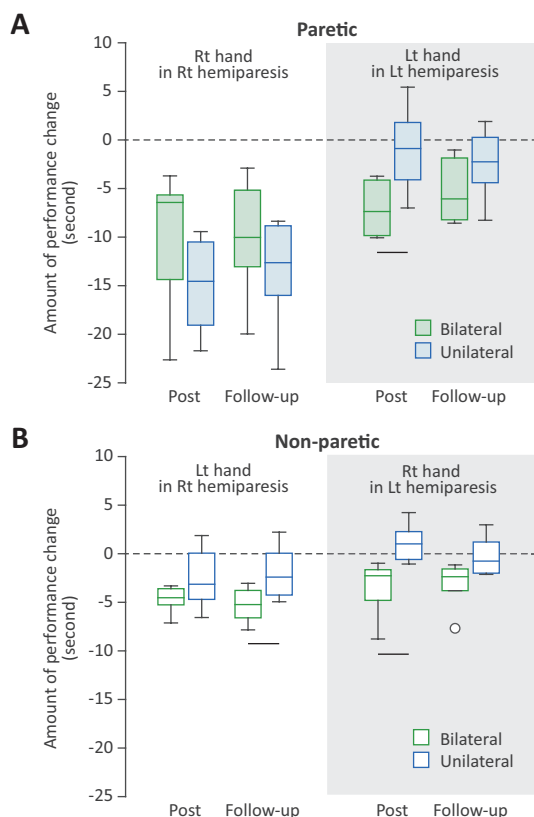
Fig. 4. Results of the sub-analysis in which the patients with left (Lt) and right (Rt) hemiparesis were analyzed separately. The graphs show the amount of change in the performance on the Nine-Hole Peg Test (NHPT) for (A) paretic and (B) non-paretic sides at the post-training (1 day after training) and follow-up (7 days after training) time-points. The left and right half-panels show the results from the patients with Rt and Lt hemiparesis, respectively. Boxplots coloured *light green* and *light blue* represent the data of the alternating bilateral training (ABT) and unilateral training (UT) groups, respectively. The *horizontal lines* below the boxplots indicate a significant difference between the ABT and UT groups ($p < 0.05$). In the right hemiparetic patients, 7 and 6 patients were assigned to the ABT and UT groups, respectively; in the left hemiparetic patients, 5 and 6 patients were assigned to the ABT and UT groups, respectively.

the sub-analysis demonstrate that repetitive training of the limb only on the paretic side would be sufficient to ensure substantial performance improvements for those with hemiparesis on the dominant side, but not for those with hemiparesis on the non-dominant side. Moreover, these findings highlight a potential benefit of ABT, specifically for those with hemiparesis on the non-dominant side, as the training effects on the paretic side were augmented.

Secondary outcome measures
Regarding the performance on the Purdue Pegboard Test and the Box and Block Test on the paretic side (Table II), the amount of change was not significantly different between the groups at either the post-training (Purdue Pegboard Test, $U = 62.0$, $Z = -0.58$, $p = 0.590$, $r = 0.12$; Box and Block Test, $U = 73.5$, $Z = 0.08$,

$p = 0.932$, $r = 0.02$) or follow-up (Purdue Pegboard Test, $U = 62.5$, $Z = -0.55$, $p = 0.590$, $r = 0.11$; Box and Block Test, $U = 83.0$, $Z = 0.64$, $p = 0.551$, $r = 0.13$) time-points. Similar results were found even when the participants with right and left hemiparesis were analyzed separately (all comparisons, $p > 0.05$, Table SI), indicating that the benefit of ABT observed for the NHPT did not generalize to the performance of different dexterity tasks. Interestingly, regarding the non-paretic side, performance on the Box and Block Test showed greater changes in the UT group than in the ABT group at the follow-up time-point ($U = 111.5$, $Z = 2.29$, $p = 0.020$, $r = 0.47$, Table II). This trend seemed to occur specifically in the participants with right hemiparesis ($U = 39.0$, $Z = 2.59$, $p = 0.008$, $r = 0.72$, Table SI). There were no significant differences between the groups for any of the other comparisons ($p > 0.05$, Tables II and SI).

Adverse events
No adverse events related to the intervention were observed throughout the study.

DISCUSSION

The current study elucidated the effects of alternating bilateral training between the non-paretic and paretic upper limbs, a more clinically relevant rehabilitation protocol that expected both trial-to-trial inter-limb transfer and use-dependent training in post-stroke patients exhibiting mild to moderate hemiparesis. Although the overall results revealed no significant benefit of ABT on upper-limb dexterity on the affected side when all participants were included, the sub-analysis revealed that ABT did improve performance on the affected side, specifically in the patients with left hemiparesis.

In patients with right hemiparesis, both the ABT and UT groups showed a similar performance improvement after the 7-day training period. In contrast, in patients with left hemiparesis, ABT led to a substantial performance improvement, whereas only a marginal change was observed after UT, highlighting the benefit of ABT in this specific patient population. It was somewhat unexpected that the performance showed little improvement, even after repetitive UT on the paretic side. One possible reason for this could be partly related to the fact that in the patients with left hemiparesis, the non-dominant side was affected. A previous study demonstrated that right-handed patients with left hemiparesis showed worse performance or improvement in motor function of the paretic upper limb than those with right hemiparesis (32). It is likely, however, that the dominance alone

did not contribute to the lower training effects, as training of the non-dominant, non-paretic side in the ABT group in those with right hemiparesis resulted in significant performance improvements (Fig. 4B, left). These results indicate that mutual interactions between the dominance and the existence of hemiparesis might contribute to the marginal performance change even after UT in patients with left hemiparesis. Importantly, even in those patients, ABT augmented the training effects on the performance of the paretic left hand, probably demonstrating the effectiveness of performing training with the dominant and non-paretic right side alternatingly with the paretic left side.

Conversely, ABT and UT both resulted in a similar performance improvement in the patients with right hemiparesis, demonstrating no clear beneficial effects of ABT in this patient population. There may be one possibility underlying this unfavourable result: lower trial-to-trial inter-limb transfer effects. It is plausible that the trial-to-trial transfer of training effects may be lessened when a transfer from the non-dominant side to the dominant side is expected. Although the reason for this kind of direction-specific difference in the transfer effects remains unclear and is still controversial, a previous study designed following the traditional inter-limb transfer model reported a difference in the transfer effects from the non-dominant side to the dominant side compared with those in the opposite direction (16).

Regarding the performance of the secondary tasks, which included the Purdue Pegboard Test and the Box and Block Test, this study found no significant differences in the performance improvements on the paretic side between the groups, which was also confirmed in the sub-analysis in which those with left and right hemiparesis were analyzed separately. Even in the ABT group in patients with left hemiparesis who benefited from the alternating training on the NHPT, no substantial improvements in performance occurred for either secondary task compared with those of the UT group, indicating that the beneficial effects of the alternating training were not directly generalizable to the performance of other dexterity tasks. One unanticipated finding was that the UT group showed greater improvement than the ABT group in the Box and Block Test on the non-paretic side. The reason for this is unclear, but it may be attributed to a difference in the baseline performance on the Box and Block Test. It is plausible that, as the performance in the UT group was worse than that in the ABT group at baseline, there remained sufficient room for improvement.

It should be noted that, although ABT expected a mixture of effects related both to the transfer of training effects from the non-paretic to the paretic limbs in a trial-to-trial manner and to use-dependent training effects of the paretic limb *per se*, the inter-limb transfer model is not the same as the traditional one. The traditional model focused on unilateral training (20), while the present model involved training alternatingly both with the non-paretic and paretic sides. The traditional inter-limb transfer has been explained by 2 potential models, bilateral access model and cross activation model (33). Briefly, the former explains that motor engrams are generated during training on one limb, stored in the central nervous system, and transferred and utilized for movement of the untrained limb. The latter is based on the idea that training on one limb activates homologous motor networks, which in turn activate both hemispheres and affect the performance of the untrained limb. We speculate that these may be potential mechanisms underlying the effectiveness of trial-to-trial transfer expected to occur in the present ABT. It is also plausible that another concept, such as "priming", may be attributed to the effect of ABT, in such a way that exposure to a preceding trial with one side affects the following trial with the other side (34).

Increased caution should be exercised when interpreting the current results, especially those of the sub-analysis, because of the small sample size used in the current pilot study. In particular, it remains unclear whether the beneficial effects of ABT were mainly attributed to left hemiparesis or paresis affecting the non-dominant side. In addition, the current findings cannot be extrapolated to all post-stroke patients with different levels of impairment, as the current study investigated only a limited number of participants based on narrow selection criteria, such that only post-stroke patients who were able to perform the NHPT within 30–60 s were included. Taken together, future studies designed with an appropriate sample size and including a sufficient number of left-handed post-stroke patients, are needed to reach a firm conclusion about the effectiveness of ABT.

The inter-limb transfer of training effects from the non-paretic side to the paretic side in post-stroke patients has been investigated in several previous studies (8–13). Many of them, however, implemented a protocol in which the participants trained only the non-paretic side, and the training effect was evaluated on the untrained, paretic side (8–12). Although such a protocol would be useful purely for verifying that inter-limb transfer can occur in post-stroke patients and could be adopted specifically for treating severely impaired patients who are incapable of sufficiently training the paretic side directly, it would not necessarily be suitable for rehabilitating patients with mild to moderate hemiparesis. The current study developed and tested a new training protocol in which participants underwent alternating training

of both the paretic and non-paretic sides, with the expectation of trial-to-trial transfer of training effect from the non-paretic to the paretic sides. The current results suggest that, especially for right-handed patients with left hemiparesis, ABT could augment the performance improvements on the paretic side. The current study provides clinicians with a potential strategy for improving hemiparetic motor function in post-stroke patients.

ACKNOWLEDGEMENTS

Supplementary material Table SI has been published as submitted. It has not been copyedited, typeset or checked for scientific content by Journal of Rehabilitation Medicine.

REFERENCES

1. Lawrence ES, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, et al. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. Stroke 2001; 32: 1279–1284.
2. Wade DT, Langton-Hewer R, Wood VA, Skilbeck CE, Ismail HM. The hemiplegic arm after stroke: measurement and recovery. J Neurol Neurosurg Psychiatry 1983; 46: 521–524.
3. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJH. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. Stroke 2003; 34: 2181–2186.
4. Kong KH, Lee J. Temporal recovery and predictors of upper limb dexterity in the first year of stroke: a prospective study of patients admitted to a rehabilitation centre. NeuroRehabilitation 2013; 32: 345–350.
5. Corbetta D, Sirtori V, Castellini G, Moja L, Gatti R. Constraint-induced movement therapy for upper extremities in people with stroke. Cochrane Database Syst Rev 2015; 10: CD004433.
6. Borges LR, Fernandes AB, Melo LP, Guerra RO, Campos TF. Action observation for upper limb rehabilitation after stroke. Cochrane Database Syst Rev 2018; 10: CD011887.
7. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol 2009; 8: 741–754.
8. Raghavan P, Krakauer JW, Gordon AM. Impaired anticipatory control of fingertip forces in patients with a pure motor or sensorimotor lacunar syndrome. Brain 2006; 129: 1415–1425.
9. Ausenda C, Carnovali M. Transfer of motor skill learning from the healthy hand to the paretic hand in stroke patients: a randomized controlled trial. Eur J Phys Rehabil Med 2011; 47: 417–425.
10. Dragert K, Zehr EP. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. Exp Brain Res 2013; 225: 93–104.
11. Urbin MA, Harris-Love ML, Carter AR, Lang CE. High-intensity, unilateral resistance training of a non-paretic muscle group increases active range of motion in a severely paretic upper extremity muscle group after stroke. Front Neurol 2015; 6: 119.
12. Sun Y, Ledwell NMH, Boyd LA, Zehr EP. Unilateral wrist extension training after stroke improves strength and neural plasticity in both arms. Exp Brain Res 2018; 236: 2009–2021.
13. Yurdakul OV, Kilicoglu MS, Rezvani A, Kucukakkas O, Eren F, Aydin T. How does cross-education affects muscles of paretic upper extremity in subacute stroke survivors? Neurol Sci 2020; 41: 3667–3675.
14. Scripture EW, Smith TL, Brown EM. On the education of muscular control and power. Studies Yale Psychol Lab 1894; 2: 114–119.
15. Schulze K, Lüders E, Jäncke L. Intermanual transfer in a simple motor task. Cortex 2002; 38: 805–815.
16. Farthing JP, Chilibeck PD, Binsted G. Cross-education of arm muscular strength is unidirectional in right-handed individuals. Med Sci Sports Exerc 2005; 37: 1594–1600.
17. Senff O, Weigelt M. Sequential effects after practice with the dominant and non-dominant hand on the acquisition of a sliding task in schoolchildren. Laterality 2011; 16: 227–239.
18. Stockel T, Weigelt M. Brain lateralisation and motor learning: selective effects of dominant and non-dominant hand practice on the early acquisition of throwing skills. Laterality 2012; 17: 18–37.
19. Coombs TA, Frazer AK, Horvath DM, Pearce AJ, Howatson G, Kidgell DJ. Cross-education of wrist extensor strength is not influenced by non-dominant training in right-handers. Eur J Appl Physiol 2016; 116: 1757–1769.
20. Manca A, Hortobagyi T, Carroll TJ, Enoka RM, Farthing JP, Gandevia SC, et al. Contralateral effects of unilateral strength and skill training: modified delphi consensus to establish key aspects of cross-education. Sports Med 2021; 51: 11–20.
21. French B, Thomas LH, Coupe J, McMahon NE, Connell L, Harrison J, et al. Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev 2016; 11: CD006073.
22. Chino N, Sonoda S, Domen K, Saitoh E, Kimura A. Stroke Impairment Assessment Set (SIAS) – A new evaluation instrument for stroke patients. Jpn J Rehabil Med 1994; 31: 119–125.
23. Domen K, Sonoda S, Chino N, Saitoh E, Kimura A. Evaluation of motor function in stroke patients using the Stroke Impairment Assessment Set (SIAS). In: Chino N, Melvin J, editors. Functional evaluation of stroke patients. Tokyo: Springer-Verlag Tokyo, 1996: p. 33–44.
24. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971; 9: 97–113.
25. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for

evaluation of physical performance. Scand J Rehabil Med 1975; 7: 13–31.

26. Mathiowetz V, Weber K, Kashman N, Volland G. Adult norms for the Nine Hole Peg Test of finger dexterity. Occup Ther J Res 1985; 5: 24–38.

27. Chen HM, Chen CC, Hsueh IP, Huang SL, Hsieh CL. Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. Neurorehabil Neural Repair 2009; 23: 435–440.

28. Ekstrand E, Lexell J, Brogardh C. Test-retest reliability and convergent validity of three manual dexterity measures in persons with chronic stroke. PM R 2016; 8: 935–943.

29. Tiffin J, Asher EJ. The Purdue pegboard; norms and studies of reliability and validity. J Appl Psychol 1948; 32: 234–247.

30. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block Test of manual dexterity. Am J Occup Ther 1985; 39: 386–391.

31. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharm Stat 2005; 4: 287–291.

32. McCombe Waller S, Whitall J. Hand dominance and side of stroke affect rehabilitation in chronic stroke. Clin Rehabil 2005; 19: 544–551.

33. Ruddy KL, Carson RG. Neural pathways mediating cross education of motor function. Front Hum Neurosci 2013; 7: 397.

34. Stoykov ME, Corcos DM, Madhavan S. Movement-based priming: clinical applications and neural mechanisms. J Mot Behav 2017; 49: 88–97.