

How robot-assisted gait training affects gait ability, balance and kinematic parameters after stroke: a systematic review and meta-analysis

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ABSTRACT

INTRODUCTION: Gait ability is often cited by stroke survivors. Robot-assisted gait training (RAGT) can help stroke patients with lower limb motor impairment regain motor coordination.

EVIDENCE ACQUISITION: PubMed, Cochrane Library, Embase were systematically searched until September 2023, to identify randomized controlled trials presenting: stroke survivors as participants; RAGT as intervention; conventional rehabilitation as a comparator; gait assessment, through scales or quantitative parameters, as outcome measures.

EVIDENCE SYNTHESIS: Twenty-seven publications involving 1167 patients met the inclusion criteria. Meta-analysis showed no significant differences in speed, cadence, spatial symmetry, and changes in joint mobility angles between the RAGT group and the control group. In addition, RAGT was associated with changes in affected side step length (SMD=0.02, 95% CI: 0.01, 0.03; P<0.0001), temporal symmetry (SMD=-0.38, 95% CI: -0.6, -0.16; P=0.0006], Six-Minute Walk Test (SMD=25.14, 95% CI: 10.19, 40.09; P=0.0010] and Functional Ambulation Categories (SMD=0.32, 95% CI: 0.01, 0.63; P=0.04). According to the PEDro scale, 19 (70.4%) studies were of high quality and eight were of moderate quality (29.6%).

moderate quality (29.6%). CONCLUSIONS: Taken together, the review synthesis showed that RAGT might have a potential role in the recovery of walking dysfunction after stroke. However, its superiority over conventional rehabilitation requires further research. Additionally, it may provide unexpected benefits that the effects of RAGT with different types or treatment protocols were further compared.

(*Cite this article as:* Chen S, Zhang W, Wang D, Chen Z. How robot-assisted gait training affects gait ability, balance and kinematic parameters after stroke: a systematic review and meta-analysis. Eur J Phys Rehabil Med 2024;60:400-11. DOI: 10.23736/S1973-9087.24.08354-0) KEY WORDS: Stroke; Walking; Gait; Meta-analysis.

Introduction

S troke is the second leading cause of death, and about 60% of stroke patients have walking dysfunction.^{1, 2} Six months after stroke, 40% of patients who had regained partial

walking ability had difficulty walking in unsupported conditions, and the rest had trouble walking in the community.^{3, 4} Besides, walking independently and safely is the most frequently cited goal of stroke survivors.⁵ Obviously, improving walking ability is also a key goal in stroke recovery.^{6, 7} Early input of the correct physiological gait pattern is conducive to the recovery of gait.⁸ As a safe, intensive and task-specific repetitive training mode, Robot-assisted Gait Training (RAGT) can help stroke patients with lower limb motor impairment regain motor coordination. RAGT not only provides high-intensity and long-duration training but also helps to reduce the workload of therapists.

Robotic devices for limb rehabilitation fall into two main categories: Exoskeletons and End-Effector robots.⁹ According to the support they apply, it is further divided into Treadmill-based RAGT (T-RAGT) and Overground RAGT (O-RAGT).¹⁰ Typically, T-RAGT is used in conjunction with a body-weight support system (BWS).¹¹ A number of studies have pointed out the effectiveness of RAGT in improving walking function.¹²⁻¹⁵ And a 2022 meta-analysis¹⁶ suggests that further randomized controlled trials comparing the efficacy of RAGT with conventional physical therapy are still warranted. As research has progressed, the scientific evidence for the benefits of RAGT may have been updated. Therefore, updating the review is indispensable. Additionally, few studies have focused on the effects of RAGT on temporal and spatial parameters.

In light of these considerations, to update the efficacy of RAGT and explore its effects on kinematic parameters, this study conducted a systematic review and meta-analysis of all extant studies on stroke.

Evidence acquisition

This systematic review and meta-analysis followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).¹⁷ And it has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42023459950).

Study selection

The principle of PICOS (population, intervention, comparison, outcome, study) was adopted to retrieve and screen articles in this study. And the inclusion criteria were as follows: 1) population: adult stroke patients diagnosed with lower limb motor dysfunction according to clinical guidelines; 2) intervention: experimental group received RAGT by exoskeleton robots or end-effectors; 3) comparison: control group received conventional training or treadmill walking training; 4) outcome: the primary outcomes were walking speed and step length, and the secondary outcomes were parameters (temporal, spatial, and temporal-spatial) and clinical scales associated with walking function in stroke; 5) study: randomized controlled study. Moreover, exclusion criteria were as follows: 1) study protocols; 2) conference summaries; 3) studies that could not isolate the efficacy of RAGT; 4) non-English literature.

Retrieval strategy

Up to September 2023, studies in PubMed, Cochrane Library and Embase were retrieved based on the PICOS principle. Medical Subject Headings (MeSH) and keywords were used to search, such as stroke*[MeSH], apoplexy [MeSH], Exoskeleton [MeSH], Robotics [MeSH], End-effector* [Title/Abstract] "gait parameter*" [Title/Abstract], walking [MeSH], etc. Accordingly, the detailed retrieval strategies are available in Supplementary Digital Material 1 (Supplementary Text File 1).

Data extraction

Two researchers (S.S. and D.Y.) conducted literature screening, data extraction and cross-verification independently. Any disagreements were resolved by discussion or sent to a third researcher (W.Y.) to judge until a consensus was reached. What is more, Endnote X9 was used to do literature management, read the titles and abstracts, eliminate obviously irrelevant literature and record the reasons and quantities. And if the literature contained multiple subgroups, the data matching the subgroups of this study were extracted. Also, we tried to contact the original author to supplement when there existed a lack of information in literature.

To summarize the effects of RAGT on walking function in stroke patients, the following data were extracted from the included studies: 1) basic information: first author, year of publication, country, etc.; 2) basic characteristics of the subjects: sample size, age, gender, stroke onset time, stroke location, etc.; 3) intervention protocols and treatment courses; 4) key elements of bias risk assessment; 5) outcome indicators.

Quality assessment

The methodological quality of the literature was assessed by the physiotherapy evidence database scale (PEDro)^{18, 19} and the Cochrane risk bias assessment tool.²⁰ Two researchers (S.S. and D.Y.) conducted the quality assessment independently. And if the results were different, they discussed and negotiated with the third researcher (W.Y.) until a consensus was reached. PEDro scale has 11 assessment items such as randomization, blinding of participants and assessors, dropout rates, etc. Moreover, the score of 7-10 is classified as high quality literature, 5-6 as medium quality literature, and \leq 4 as low quality literature.²¹

Statistical analysis

Two statistical software, RevMan 5.4 and Stata15, were used for meta-analysis.

Effect size

The mean and standard deviation value were combined to calculate the mean difference due to the outcome indicators are continuous variables with the same unit. And 95%CI are given for each effect size. The median and quartile values of the included studies were converted to mean or standard deviation according to the formula and then combined for analysis.^{22, 23}

Heterogeneity

I² statistic was used for evaluation. Its value represents small (25% or lower), medium or large (75% or higher) heterogeneity.²⁴ A I² threshold of 50% was set to evaluate heterogeneity across studies. If I² \geq 50%, it indicated the application of a random effect model for data analysis, otherwise, the fixed effects model was employed. To identify the sources of heterogeneity, subgroup analyses were conducted based on post-stroke time (acute phase [≤ 6 months], subacute phase and chronic phase [≥ 6 months]) or robot training type (O-RAGT and T-RAGT).

Sensitivity analysis

Stata/SE was used to conduct a meta-analysis after removing individual studies successively, and evaluate the differences between the eliminated results and the original combined results.

Publication bias was directly judged by drawing funnel plot.

Evidence synthesis

Study selection

A total of 5965 studies (1892 from PubMed, 950 from Cochrane Library and 3123 from Embase) were retrieved using the above retrieval strategies. Duplicate literature was eliminated and simultaneously the remaining literature was screened. Only 27 studies²⁵⁻⁵¹ which met our stringent criteria were finally included. A total of 1167 patients were included in the study cohort (607 in the experimental group and 560 in the control group) and their basic information is shown in Supplementary Digital Material 2 (Supplementary Table I). In addition, Figure 1 shows the literature screening process and results in detail. Only two

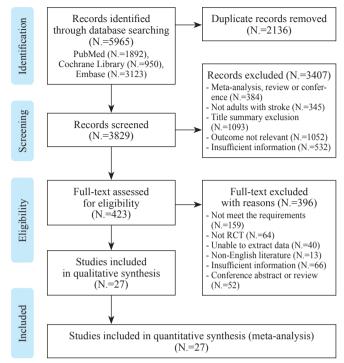


Figure 1.-Literature screening process and results.

studies^{28, 35} combined RAGT with Conventional gait training (CGT) while others were single RAGT. Moreover, in 85% of the included studies, treatment cycles were greater than or equal to four weeks, with a single treatment duration ranging from twenty minutes to one hour.

Risk of bias

Figure 2 and Table I display the risk of bias in the included studies.²⁵⁻⁵¹ Among them, eight studies^{25, 26, 31, 40, 41, 43, 44, 51} not explicitly stated whether blind method was used, one study³³ did not use blind method, 15 studies^{27-30, 32, 35, 37-39, 45-50} used single blind method, one study³⁶ used double blind method, and two studies^{34, 42} used triple blind method. As for random sequence generation, only three studies^{32, 34, 40} have unclear random sequence generation methods, and the rest have clear descriptions. Meanwhile, nine studies^{26, 27, 31-33, 40, 43, 44, 49} did not mention allocation hiding, while the rest had detailed descriptions. Moreover, data were completely reported in all studies. The majority of studies had no other risk of bias or were unclear, and only one study³⁹ was defined as high risk due to the availability of Research and development funding. According to the PEDro score, there were 8 medium-quality and 19 high-quality studies.

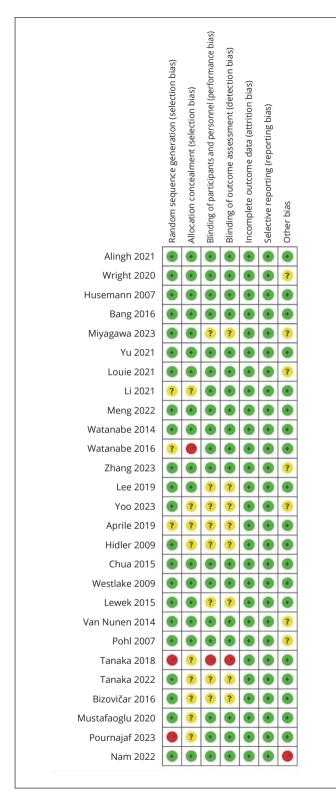


Figure 2.—Cochrane bias risk score.

Results of individual studies

Walking speed

Thirteen studies were included, involving 509 subjects with lower limb dysfunction after stroke. Due to the heterogeneity test results (P<0.00001, I²=94%), a random effect model analysis was used. And as shown in Figure 3A, the results indicated that there was no significant statistical difference between the experimental group and the control group (SMD=0.06, 95% CI: -0.02, 0.14; P=0.14). Sensitivity analysis found that the results showed satisfactory robustness, as shown in Figure 4A.

Subgroup analysis of robot training type indicated that O-RAGT (SMD=0.11, 95% CI: 0.01, 0.21; P=0.03) showed a higher effect size than T-RAGT (SMD=0.04, 95% CI: -0.05, 0.13; P=0.38), as shown in Figure 3A.

Cadence

Thirteen studies were included, including 511 patients with lower limb dysfunction after stroke. Due to the heterogeneity test results (P<0.00001, I²=81%), a random effect model analysis was used. And as shown in Figure 3B, the results reflected that there was no significant statistical difference between the experimental group and the control group (SMD=2.04, 95% CI: -2.51, 6.60; P=0.38). Sensitivity analysis pointed out that the results showed satisfactory robustness after removing Joseph,⁴³ as shown in Figure 4B.

Subgroup analysis of robot training type indicated that O-RAGT (SMD=7.29, 95% CI: 1.09, 13.49; P=0.02] showed a higher effect size than T-RAGT (SMD=-0.24, 95% CI: -5.99, 5.51; P=0.93, as shown in Figure 3B.

Affected side step length

Six studies were included, involving 266 patients with lower limb dysfunction after stroke. On account of the heterogeneity test results (P=0.38, I²=6%), a fixed effect model analysis was used. And as shown in Figure 5A, the results indicated that there was a statistical difference between the experimental group and the control group (SMD=0.02, 95% CI: 0.01, 0.03; P<0.0001).

Non-affected side step length

Three studies were included, involving 93 patients with lower limb dysfunction after stroke. On account of the heterogeneity test results (P=0.72, I²=0%), a fixed effect model analysis was used. And as shown in Figure 5B, the results indicated that there was no statistical difference

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Inclusion study	1	2	3	4	5	6	7	8	9	10	11	Total
Alingh ²⁸	\checkmark									\checkmark		8
Wright ²⁹				\checkmark						\checkmark	\checkmark	8
Husemann ³⁵				\checkmark						\checkmark		8
Bang ³⁶	\checkmark		\checkmark	\checkmark		\checkmark		\checkmark	\checkmark	\checkmark	\checkmark	9
Miyagawa ⁴¹				\checkmark						\checkmark		7
Yu ⁴⁸				\checkmark						\checkmark	\checkmark	8
Louie ³⁸				\checkmark						\checkmark		8
Li ³²	\checkmark									\checkmark	\checkmark	6
Meng ³⁰												8
Watanabe 42	\checkmark									\checkmark	\checkmark	10
Watanabe ³⁴												8
Zhang ⁵⁰										\checkmark	\checkmark	8
Lee 51												7
Yoo ²⁶	\checkmark											6
Aprile ⁴⁰												5
Hidler 43										\checkmark	\checkmark	6
Chua ³⁷												8
Westlake ⁴⁵	\checkmark											8
Lewek ²⁵												7
Van Nunen 46												8
Pohl ⁴⁷										\checkmark	\checkmark	8
Fanaka 31												6
Bizovičar ⁴⁴												6
Mustafaoglu ²⁷										\checkmark	\checkmark	7
Pournajaf ⁴⁹												6
Tanaka 33												5
Nam ³⁹							V					8

1: eligibility criteria; 2: randomly allocated; 3: assigning concealment; 4: similar at baseline; 5: blinding of all subjects; 6: blinding of all therapists; 7: blinding of all assessors; 8: measures of at least one key outcome; 9: intention to treat; 10: comparison between groups; 11: point measures and measures of variability.

between the experimental group and the control group (SMD=0.02, 95% CI: -0.05, 0.09; P=0.56).

Symmetry

It can be divided into spatial symmetry and temporal symmetry.

Regarding spatial symmetry, four studies were included, involving 119 patients with lower limb dysfunction after stroke. Due to the heterogeneity test results (P=0.12, $I^{2}=49\%$), a fixed effect model analysis was used. And as shown in Figure 6A, the results indicated that there was no statistical difference between the experimental group and the control group (SMD=0.00, 95% CI: -0.10, 0.11; P=0.98).

Regarding temporal symmetry, five studies were included, involving 140 patients with lower limb dysfunction after stroke. On account of the heterogeneity test results (P=0.02, I²=65%), a random effect model analysis was used. And as shown in Figure 6B, the results indicated that there was a statistical difference between the experimental group and the control group (SMD=-0.38, 95% CI: -0.6, -0.16; P=0.0006).

Six-Minute Walk Test (6MWT)

Sixteen studies were included, involving 813 patients with lower limb dysfunction after stroke. Due to the heterogeneity test results (P=0.0010, I²=60%), a random effect model analysis was used. And as shown in Figure 7A, the results indicated that there was a statistical difference between the experimental group and the control group (SMD=25.14, 95% CI: 10.19, 40.09; P=0.0010). Sensitivity analysis reminded that the results showed satisfactory robustness after eliminating Rustem²⁷ and Sanaz,⁴⁹ as shown in Figure 4C.

Subgroup analysis of stroke onset time reflected that acute phase (SMD=37.80, 95% CI: 39.81, 45.78; P<0.00001) showed a better effect size than subacute or chronic phase (SMD=1.68, 95% CI: -8.72, 12.07; P=0.75), as shown in Figure 7A.

Berg Balance Scale (BBS)

Nine studies were included, including 298 patients with lower limb dysfunction after stroke. Due to the heterogeneity test results (P=0.43, I²=1%), a fixed effect model analysis was used. And as shown in Figure 7B, the results

Study or Subgroup	Mean	erimenta SD	al Total		ontrol SD	Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
2.8.1 O-RAGT							Constanting of the second seco		
Alingh, Jf2021	0.34	0.32	13	0.19	0.34	13	5.3%	0.15 [-0.10, 0.40]	
Daichi Miyagawa2023	0.24	0.29	17	0.15	0.3	18	6.9%	0.09 [-0.11, 0.29]	
Hwang-Jae Lee2019	0.29	0.24	14	0.18	0.13	12	8.6%	0.11 [-0.04, 0.26]	++
Irene Aprilea2019	0.31	0.82	14	0.06	1	12	1.1%	0.25 [-0.46, 0.96]	
Naojiro Tanaka2018	0.095	0.43	21	0.036	0.59	20	4.0%	0.06 [-0.26, 0.38]	
Subtotal (95% CI)	0.000	0.45	79	0.030	0.55	75	25.8%	0.11 [0.01, 0.21]	•
Heterogeneity: Tau ² = 0.	nn chi	- 0.20 4		- 0.00)	12-09		2010.11	and fore it are if	-
Test for overall effect Z =				= 0.30)					
2.8.2 T-RAGT									
Britta Husemann2007	0.06	0.026	16	0.08	0.044	14	12.3%	-0.02 [-0.05, 0.01]	
Dae-Hyouk Bang2016		0.046	9	0.09	0.04	9	12.0%	0.07 [0.03, 0.11]	*
Deng Yu2021	0.069	0.37	27	0.03	0.32	27	7.2%	0.04 [-0.15, 0.22]	
Guilin Mena2022	0.33	0.22	62	0.2	0.19	61	11.2%	0.13 [0.06, 0.20]	+
	0.33	0.22	18			16	8.8%		
Huihuang Zhang 2023				0.02	0.19		12.4%	0.26 [0.12, 0.40]	
Joseph Hidler2009	0.12		33		0.03	30		-0.13 [-0.14, -0.12]	
Kelly P Westlake2009	0.1	0.35	8	0.03	0.29	8	4.0%	0.07 [-0.24, 0.38]	
Michael D. Lewek2015	0.01	0.21	9	0.06	0.24	8	6.3%	-0.05 [-0.27, 0.17]	
Subtotal (95% CI)			182			173	74.2%	0.04 [-0.05, 0.13]	
Heterogeneity: Tau ² = 0. Test for overall effect: Z =			, df = 7	(P < 0.0	00001);	l ² = 96	%		
Total (95% CI)			261			248	100.0%	0.06 [-0.02, 0.14]	•
Heterogeneity: Tau ² = 0.	01 Chill	= 188 49		2 (P < 0	00001				1 1 1 1 1
Test for overall effect Z =				- (1 - 0			+ 10		-1 -0.5 0 0.5 1
Test for subaroup differe			40-0	10-0	242 17-	1 701			[control] [experimental]
	Ai	nalys	sis (of w	alki	ng	spee	d and its su	bgroups
	Exp	eriment	al	(Control	0		Mean Difference	Mean Difference
Study or Subgroup		eriment	al		Control	0	Spee Weight		0
2.12.1 O-RAGT	Exp Mean	erimenta SD	al Total	(Mean	Control SD	Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference
2.12.1 O-RAGT Daichi Miyagawa2023	Exp Mean 13.5	eriment SD 13.68	al <u>Total</u> 17	Mean 6.7	Control SD 15.92	Total	Weight 9.1%	Mean Difference IV, Random, 95% Cl 6.80 [-3.02, 16.62]	Mean Difference
2.12.1 O-RAGT Daichi Miyagawa2023 Dong-Xia Li2021	Exp Mean 13.5 20.41	eriment: SD 13.68 17.38	al <u>Total</u> 17 17	(Mean 6.7 10.18	Control SD 15.92 20	<u>Total</u> 18 15	9.1% 6.9%	Mean Difference IV, Random, 95% Cl 6.80 [-3.02, 16.62] 10.23 [-2.84, 23.30]	Mean Difference
2.12.1 O-RAGT Daichi Miyagawa2023 Dong-Xia Li2021 Hiroki Watanabe2014	Exp Mean 13.5 20.41 22.3	erimenta SD 13.68 17.38 34.67	al <u>Total</u> 17 17 11	6.7 10.18 19.7	Control SD 15.92 20 33.3	Total 18 15 11	Weight 9.1% 6.9% 2.2%	Mean Difference IV, Random, 95% Cl 6.80 [-3.02, 16.62] 10.23 [-2.84, 23.30] 2.60 [-25.81, 31.01]	Mean Difference
2.12.1 O-RAGT Daichi Miyagawa2023 Dong-Xia Li2021 Hiroki Watanabe2014 Hiroki Watanabe2016	Exp Mean 13.5 20.41 22.3 26.9	13.68 17.38 34.67 34.85	al <u>Total</u> 17 17 17 11 12	6.7 10.18 19.7 23.6	Control SD 15.92 20 33.3 33.05	Total 18 15 11 12	9.1% 6.9% 2.2% 2.4%	Mean Difference IV. Random, 95% Cl 6.80 [-3.02, 16.62] 10.23 [-2.84, 23.30] 2.60 [-26.81, 31.01] 3.30 [-23.87, 30.47]	Mean Difference
2.12.1 O-RAGT Daichi Miyagawa2023 Dong-Xia Li2021 Hiroki Watanabe2014 Hiroki Watanabe2016 Hwang-Jae Lee2019	Exp Mean 13.5 20.41 22.3 26.9 28.28	13.68 17.38 34.67 34.85 26.421	al Total 17 17 17 11 12 14	6.7 10.18 19.7 23.6 13.04	Control SD 15.92 20 33.3 33.05 24.37	Total 18 15 11 12 12	9.1% 6.9% 2.2% 2.4% 4.0%	Mean Difference IV, Random, 95% CI 6.80 [-3.02, 16.62] 10.23 [-2.84, 23.30] 2.60 [-25.81, 31.01] 3.30 [-23.87, 30.47] 15.24 [-4.30, 34.78]	Mean Difference
2.12.1 O-RAGT Daichi Miyagawa2023 Dong-Xia Li2021 Hiroki Watanabe2014 Hiroki Watanabe2016 Hwang-Jae Lee2019 Irene Aprilea2019	Exp Mean 13.5 20.41 22.3 26.9 28.28 2.5	erimenti SD 13.68 17.38 34.67 34.85 26.421 33.9	al Total 17 17 17 11 12 14 14	6.7 10.18 19.7 23.6 13.04 2.85	Control SD 15.92 20 33.3 33.05 24.37 34.39	Total 18 15 11 12 12 12	9.1% 6.9% 2.2% 2.4% 4.0% 2.5%	Mean Difference IV, Random, 95% CI 6.80 [-3.02, 16.62] 10.23 [-2.84, 23.30] 2.60 [-2.63, 31.01] 3.30 [-2.3.87, 30.47] 15.24 [-4.30, 34.78] -0.35 [-2.68, 25.59]	Mean Difference
2.12.1 O-RAGT Daichi Miyagawa2023 Dong-Xia Li2021 Hiroki Watanabe2014 Hiroki Watanabe2016 Hwang-Jae Lee2019 Irene Aprilea2019 Naojiro Tanaka2018	Exp Mean 13.5 20.41 22.3 26.9 28.28	13.68 17.38 34.67 34.85 26.421	al Total 17 17 17 11 12 14 14 14 21	6.7 10.18 19.7 23.6 13.04 2.85	Control SD 15.92 20 33.3 33.05 24.37	Total 18 15 11 12 12 12 20	Weight 9.1% 6.9% 2.2% 2.4% 4.0% 2.5% 4.6%	Mean Difference N, Random, 95% CI 6.80 [-3.02, 16.62] 10.23 [-2.64, 23.30] 2.60 [-26.81, 31.01] 3.30 [-23.87, 30.47] 1.5.24 [-4.30, 34.78] -0.35 [-26.69, 25.99] 3.82 [-14.16, 21.80]	Mean Difference
2.12.1 O-RAGT Daichi Miyagawa2023 Dong-Xia Li2021 Hiroki Watanabe2014 Hiroki Watanabe2016 Hwang-Jae Lee2019 Irene Aprilea2019 Naojiro Tanaka2018 Subtotal (55% CI)	Exp Mean 13.5 20.41 22.3 26.9 28.28 2.5 4.14	13.68 17.38 34.67 34.85 26.421 33.9 24.98	al Total 17 17 11 12 14 14 14 21 106	6.7 10.18 19.7 23.6 13.04 2.85 0.32	15.92 20 33.3 33.05 24.37 34.39 33.01	Total 18 15 11 12 12 12 20 100	9.1% 6.9% 2.2% 2.4% 4.0% 2.5%	Mean Difference IV, Random, 95% CI 6.80 [-3.02, 16.62] 10.23 [-2.84, 23.30] 2.60 [-2.63, 31.01] 3.30 [-2.3.87, 30.47] 15.24 [-4.30, 34.78] -0.35 [-2.68, 25.59]	Mean Difference
2.12.1 O-RAGT Daichi Myagawa2023 Dong-Xia Li201 Hiroki Watanabe2014 Hiroki Watanabe2016 Hwang-Jae Lee2019 Itene Aprilea2019 Naojiro Tanaka2018 Subtotal (95% CI) Heterogenelty: Tau ^a = 0.1	Exp Mean 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi#=	eriment SD 13.68 17.38 34.67 34.85 26.421 33.9 24.98 = 1.49, df	al Total 17 17 11 12 14 14 14 21 106	6.7 10.18 19.7 23.6 13.04 2.85 0.32	15.92 20 33.3 33.05 24.37 34.39 33.01	Total 18 15 11 12 12 12 20 100	Weight 9.1% 6.9% 2.2% 2.4% 4.0% 2.5% 4.6%	Mean Difference N, Random, 95% CI 6.80 [-3.02, 16.62] 10.23 [-2.64, 23.30] 2.60 [-26.81, 31.01] 3.30 [-23.87, 30.47] 1.5.24 [-4.30, 34.78] -0.35 [-26.69, 25.99] 3.82 [-14.16, 21.80]	Mean Difference
2.12.10-RAGT Daichi Myagawa2023 Dong-Xia Li2021 Hiroki Watanabe2014 Hiroki Watanabe2016 Hwang-Jae Le2019 Irene Aprilea2019 Nagiro Tanaka2018 Subtotal (95% C) Heterogeneity. Tau ² = 0.1 Test for overall effect. Z =	Exp Mean 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi#=	eriment SD 13.68 17.38 34.67 34.85 26.421 33.9 24.98 = 1.49, df	al Total 17 17 11 12 14 14 14 21 106	6.7 10.18 19.7 23.6 13.04 2.85 0.32	15.92 20 33.3 33.05 24.37 34.39 33.01	Total 18 15 11 12 12 12 20 100	Weight 9.1% 6.9% 2.2% 2.4% 4.0% 2.5% 4.6%	Mean Difference N, Random, 95% CI 6.80 [-3.02, 16.62] 10.23 [-2.64, 23.30] 2.60 [-26.81, 31.01] 3.30 [-23.87, 30.47] 1.5.24 [-4.30, 34.78] -0.35 [-26.69, 25.99] 3.82 [-14.16, 21.80]	Mean Difference
2.12.1 O-RAGT Daichi Miyagawa2023 Dong-Xia Li2021 Hiroki Watanabe2014 Hiroki Watanabe2016 Hwang-Jae Lee2019 Irene Aprilea2019 Naojiro Tanaka2018	Exp Mean 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi#=	eriment SD 13.68 17.38 34.67 34.85 26.421 33.9 24.98 = 1.49, df	al <u>Total</u> 17 17 11 12 14 21 106 = 6 (P	6.7 10.18 19.7 23.6 13.04 2.85 0.32	15.92 20 33.3 33.05 24.37 34.39 33.01	Total 18 15 11 12 12 12 20 100	Weight 9.1% 6.9% 2.2% 2.4% 4.0% 2.5% 4.6% 31.6%	Mean Difference M. Randem, 95% CI 6.80 [-3.02, 16.62] 10.23 [-2.84, 23.03] 2.60 [-2.681, 31.01] 3.30 [-2.387, 30.47] -0.35 [-2.69, 2.599] 3.82 [+4.16, 21.80] 7.29 [1.09, 13.49]	Mean Difference
2.12.10.4Rof Daichi Miyagawa2023 Dong-Xia L2021 Hiroki Watanabe 2014 Hiroki Watanabe 2016 Hwang-Jae Lee2019 Inagiro Tanaka2018 Subtotal (95% Cf) Heterogeneity: Tau ² = 0.1 Test for overall effect Z = 2.12.2.T.RAGT Britta Husemann2007	Exp Mean 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi [#] = 2.30 (P 7.38	13.68 17.38 34.67 34.85 26.421 33.9 24.98 = 1.49, df = 0.02) 4.05	al <u>Total</u> 17 17 11 12 14 21 106 = 6 (P 16	(<u>Mean</u> 6.7 10.18 19.7 23.6 13.04 2.85 0.32 = 0.96); 11.78	Control SD 15.92 20 33.3 33.05 24.37 34.39 33.01 F = 0% 5.71	Total 18 15 11 12 12 20 20 100	Weight 9.1% 6.9% 2.2% 2.4% 4.0% 2.5% 4.6% 31.6%	Mean Difference <u>IV</u> , Randem, 95% CI 6.00, 19.02, 16.62, 1 0.23 (-24, 22.30) 2.60 (-25.61, 31.01) 3.30 (-25.61, 31.01) 3.30 (-25.61, 31.01) 3.30 (-25.61, 31.01) 3.32 (-14.16, 25.91) 3.32 (-14.16, 25.91) 7.29 (1.09, 13.49) -4.40 (-7.99, -0.81)	Mean Difference
2.12.10.FAGT Daichi Miyagawa2023 Dong-Xia L2021 Hiroki Watanabe2014 Hiroki Watanabe2016 Hivang-Jae Leo2019 Naojiro Tanaka2018 Subtota (95% CI) Heterogeneliy: Tau ²⁺ D.1 Test for overall effect: Z = 2.12.2.T.RAGT Britta Husemann2007 Dae-Hyouk Bang2018	Exp Mean 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi [#] = 2.30 (P 7.38 5.39	erimenti SD 13.68 17.38 34.65 26.421 33.9 24.98 = 1.49, df = 0.02) 4.05 1.67	al <u>Total</u> 17 17 11 12 14 14 21 106 = 6 (P 16 9	(Mean 6.7 10.18 19.7 23.6 13.04 2.85 0.32 = 0.95); 11.78 2.46	Control SD 15.92 20 33.3 33.05 24.37 34.39 33.01 ₱ = 0% 5.71 1.85	Total 18 15 11 12 12 12 20 100	Weight 9.1% 6.9% 2.2% 2.4% 4.6% 31.6% 14.3% 15.4%	Mean Difference IV. Random, 95% CI 6.80 [3.02, 16.62] 10.03 [2.64 (2.63) 10.03 [2.64 (2.63) 13.04 (2.37) 15.24 (4.30, 34.74) 15.24 (4.30, 34.76) 3.82 [14.16, 21.80] 7.29 [1.09, 13.49] -4.40 [7.99, 0.81] 2.93 [1.30, 4.56]	Mean Difference
2.12.10-RAGT Dolichi Myagawa2023 Dong-Xia Li2021 Hiroki Watanabe 2014 Hiroki Watanabe 2016 Hivang-Jae Leo2019 Inena Aprilea2019 Nagliro Tanaka2018 Subtotal (95% CI) Heterogeneity: Tau" = 0.1 Test for overall effect z = 2.12.2.T-RAGT Britla Husemann2007 Dae-Hyouk Bang2016 Deng Yu2021	Exp <u>Mean</u> 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi [#] = 2.30 (P 7.38 5.39 2.75	erimenta 5D 13.68 17.38 34.67 34.85 26.421 33.99 24.98 = 1.49, df = 0.02) 4.05 1.67 25.68	al Total 17 17 11 12 14 14 21 106 6 (P 16 9 27	(Mean 6.7 10.18 19.7 23.6 13.04 2.85 0.32 = 0.95); 11.78 2.46 -2.36	Control SD 15.92 20 33.3 33.05 24.37 34.39 33.01 F = 0% 5.71 1.85 13.96	Total 18 15 11 12 12 12 20 100	Weight 9.1% 6.9% 2.2% 2.4% 4.0% 2.5% 31.6% 31.6%	Mean Difference IX. Bandom, 85% CI 6.80 1-30 2, 16.82 10.23 (-24, 23.30) 2.60 (-25.81, 31.01) 0.36 (-25.81, 31.01) 0.36 (-25.80, 25.00) 0.38 (-24.60, 25.00) 3.82 (-14.61, 21.80) 7.29 (1.09, 13.49) -4.40 (-7.99, -0.81) 2.93 (1.30, 4.56) 5.11 (-5.32, 16.14)	Mean Difference
2.12.10.RAGT Daichi Myagawa2023 Dong-Xia Li2021 Hiroki Watanabe 2014 Hiroki Watanabe 2014 Hiroki Watanabe 2019 Imena Aprilea2019 Naajiro Tanaka2018 Subtotat (19%) auf = 0.1 Heterogeneity, Tau ² = 0.1 Heterogeneity, Tau ² = 0.1 Heterogeneity, Tau ² = 0.1 Past for overail effect Z = 2.12.2.T.RAGT Britta Husemann2007 Dae-Hyouk Bang2018 Deng Yu2021 Guilin Meng2022	Exp <u>Mean</u> 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi [#] = 2.30 (P 7.38 5.39 2.75 16.57	erimenti SD 13.68 17.38 34.67 34.85 26.421 33.9 24.98 = 1.49, df = 0.02) 4.05 1.67 25.68 15.98	al <u>Total</u> 17 17 11 12 14 14 11 106 6 (P 16 9 9 9 27 62	(<u>Mean</u> 6.7 10.18 19.7 23.66 13.04 2.85 0.32 = 0.96); 11.78 2.46 -2.36 9.9	5.71 15.92 20 33.3 33.05 24.37 34.39 33.01 ₽ = 0%	Total 18 15 11 12 12 12 20 100 14 9 27 61	Weight 9.1% 6.9% 2.2% 2.4% 4.0% 2.5% 4.6% 31.6%	Mean Difference M. Bandom, B5% CI 6.30 (-20, 216.62) 10.23 (-244, 23.0) 2.30 (-25.84, 31.01) 3.30 (-23.47, 30.47) -0.35 (-25.49, 25.30) 7.28 (1.09, 13.48) 7.28 (1.09, 13.48) -4.40 (-7.99, -0.81) 2.93 (1.30, 4.58) 5.11 (-5.21, 61.40) 6.67 (1.03, 12.31)	Mean Difference
2.12.10.4Rdf Daichi Mysgawa2023 Dong-Xiki Li2021 Hiroki Watanabe 2014 Hiroki Watanabe 2014 Hiroki Watanabe 2016 Hiroki Againabe 2019 Nanjiro Tanaka2018 Subtotal (95% CI) Heterogeneity: Tau ⁺ = 0.1 Testfor overall effect Z = 2.12.2.T.RAGT Britla Husemann2007 Dae-Hyouk Bang2016 Daehyouk Bang2016 Daehyouk Bang2016 Qualin Meng2022 Joseph Hilder2009	Exp Mean 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi [#] = 2.30 (P 7.38 5.39 2.75 16.57 5.5	sp 13.68 17.38 34.67 34.85 26.421 33.9 24.98 = 1.49, df = 0.02) 4.05 1.67 25.68 15.98 5.3	al <u>Total</u> 17 17 11 12 14 14 14 106 6 (P 16 9 27 62 33	((<u>Mean</u> 6.7 10.18 19.7 2.36 0.32 = 0.96); 11.78 2.46 9.9 13.7	Control SD 33.3 33.05 33.01 7=0% 5.71 1.856 15.92 6	Total 18 15 11 12 12 20 100 14 9 9 27 61 30	Weight 9.1% 6.9% 2.4% 4.0% 2.5% 4.6% 31.6% 14.3% 8.2% 12.7% 14.8%	Mean Difference IX, Bandem, 95% CJ 6.0213 (2.24, 23.01) 2.601 (2.63, 13.01) 2.601 (2.63, 13.01) 1.524 (4.30, 34.76) 3.82 (4.4.30, 34.76	Mean Difference
2.12.10.4RdGT Datich Myagaw2023 Dong Xiel L2021 Hirold Watanake2016 Hirold Watanake2016 Hirold Watanake2016 NadjioT Tanake2018 NadjioT Tanake2018 NadjioT Tanake2018 NadjioT Tanake2018 Hietrogenenity: Tari 2 2.12.2 T.RAGT Birtla Husemann2007 Dae-Hyouk Bang2016 Deng Yu2021 Guilin Meng2022 Joseph Hietrog202 Joseph Hietrog202	Exp <u>Mean</u> 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi [#] = 2.30 (P 7.38 5.39 2.75 16.57	erimenti SD 13.68 17.38 34.67 34.85 26.421 33.9 24.98 = 1.49, df = 0.02) 4.05 1.67 25.68 15.98	al <u>Total</u> 17 17 11 12 14 14 14 14 21 106 6 (P 16 9 27 62 33 9	((<u>Mean</u> 6.7 10.18 19.7 2.36 0.32 = 0.96); 11.78 2.46 9.9 13.7	5.71 15.92 20 33.3 33.05 24.37 34.39 33.01 ₽ = 0%	Total 18 15 11 12 12 12 12 12 12 100 100	Weight 9.1% 6.9% 2.4% 4.0% 2.5% 4.0% 31.6% 14.3% 15.4% 8.2% 12.7% 14.8% 2.9%	Mean Difference M. Bandom, 85×G. 1 6.30 (-3.0.2, 16.2) 10.23 (-2.44, 2.30) 10.33 (-2.44, 2.30) 13.30 (-2.34, 7.30, 7.4) 13.30 (-2.34, 7.30, 7.4) 13.32 (-2.34, 7.30, 7.2) 13.32 (-1.44, 6.21, 80) 7.29 (1.09, 13.49) 2.35 (1.30, 4.59) 5.11 (-5.32, 16.14) 6.67 (10.3, 12.31) -2.00 (-2.61, 5.2, 21.5)	Mean Difference
2.12.10.4Rdf Dachk Myagaw2023 Dong Xiel L0201 Hiroki Watanabe2014 Hiroki Watanabe2014 Hiroki Watanabe2016 Hiroki Atanabe2016 Hiroki Atanabe2018 Stabdal (95% C) Dach-Youki Bang2016 Dachyoki Bang2010 Dach-Youki Bang2010 Dachyoki B	Exp Mean 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; Chi#= = 2.30 (P 7.38 5.39 2.75 18.57 5.5 0	13.68 17.38 34.67 34.85 26.421 33.9 24.98 = 1.49, df = 0.02) 4.05 1.67 25.68 15.98 5.3 24	al <u>Total</u> 17 17 11 12 14 14 14 21 106 6 9 27 62 33 3 9 156	(<u>Mean</u> 6.7 10.18 13.04 2.85 0.32 = 0.96); 11.78 2.46 6.99 13.7 2	SD 15.92 20 33.3 33.05 24.37 33.01 15.92 24.37 33.01 14.39 5.711 1.85 13.96 15.92 6 26.51	Total 18 15 11 12 12 20 100 100 14 9 27 61 30 8 149	Weight 9.1% 6.9% 2.2% 2.4% 4.0% 2.5% 34.6% 31.6% 14.3% 15.4% 8.2% 12.7% 14.8% 2.9% 68.4%	Mean Difference IX, Bandem, 95% CJ 6.0213 (2.24, 23.01) 2.601 (2.63, 13.01) 2.601 (2.63, 13.01) 1.524 (4.30, 34.76) 3.82 (4.4.30, 34.76	Mean Difference
2.12.10.4RdGT Datich Myagaw2023 Dong Xiel L2021 Hirold Watanake2016 Hirold Watanake2016 Hirold Watanake2016 NadjioT Tanake2018 NadjioT Tanake2018 NadjioT Tanake2018 NadjioT Tanake2018 Hietrogenenity: Tari 2 2.12.2 T.RAGT Birtla Husemann2007 Dae-Hyouk Bang2016 Deng Yu2021 Guilin Meng2022 Joseph Hietrog202 Joseph Hietrog202	Exp Mean 13.5 20.41 22.3 28.9 28.28 2.5 4.14 00; Chi [#] = 2.30 (P 7.38 5.39 2.75 16.57 0 1.01; Chi [#]	erimenti SD 13.68 17.38 34.67 34.85 26.421 33.9 24.98 = 1.49, df = 0.02) 4.05 1.67 25.68 15.98 15.98 5.3 24	al <u>Total</u> 17 17 11 12 14 14 14 21 106 6 9 27 62 33 3 9 156	(<u>Mean</u> 6.7 10.18 13.04 2.85 0.32 = 0.96); 11.78 2.46 6.99 13.7 2	SD 15.92 20 33.3 33.05 24.37 33.01 15.92 24.37 33.01 14.39 5.711 1.85 13.96 15.92 6 26.51	Total 18 15 11 12 12 20 100 100 14 9 27 61 30 8 149	Weight 9.1% 6.9% 2.2% 2.4% 4.0% 2.5% 34.6% 31.6% 14.3% 15.4% 8.2% 12.7% 14.8% 2.9% 68.4%	Mean Difference M. Bandom, 85×G. 1 6.30 (-3.0.2, 16.2) 10.23 (-2.44, 2.30) 10.33 (-2.44, 2.30) 13.30 (-2.34, 7.30, 7.4) 13.30 (-2.34, 7.30, 7.4) 13.32 (-2.34, 7.30, 7.2) 13.32 (-1.44, 6.21, 80) 7.29 (1.09, 13.49) 2.35 (1.30, 4.59) 5.11 (-5.32, 16.14) 6.67 (10.3, 12.31) -2.00 (-2.61, 5.2, 21.5)	Mean Difference
2.12.10.4RdGT Daticki Mysgaw2023 Dong Xiba L2021 Hiroki Wistanabe 2014 Hiroki Wistanabe 2014 Hiroki Wistanabe 2014 Hiroki Qattanabe 2016 Hiroki Qattanabe 2016 Hiroki Qattanabe 2016 Hiroki Qattanabe 2016 Hiroki Qattanabe 2016 Date Xiba Qattanabe 2016 Hiroki Qattanabe 2	Expe Mean 13.5 20.41 22.3 26.9 2.5 4.14 00; Chi [#] = 2.30 (P 7.38 5.39 2.75 5.39 2.75 5.39 2.75 5.39 0.01; Chi [#] = 0.08 (P	talent so so so so so so so so so so	al <u>Total</u> 17 17 11 12 14 21 106 6 (P 166 9 27 62 33 3 9 156 df = 5 262	(<u>Mean</u> 6.7 10.18 19.7 23.6 13.04 2.85 0.32 = 0.96); 11.78 2.46 -2.36 9.9 13.7 2 (P < 0.0	Control SD 15.92 20 33.3 33.05 24.37 34.39 33.01 1.85 5.71 1.85 5.71 1.96 5.71 1.96 6 26.51 00001); 1	Total 18 15 11 12 12 20 100 14 9 27 61 30 8 149 919 249	Weight 9.1% 5.9% 2.2% 2.4% 2.5% 4.0% 3.5% 31.6% 14.3% 15.4% 8.2% 12.7% 14.8% 2.9% 68.4% 6	Mean Difference M. Bandom, 85×G. 1 6.30 (-3.0.2, 16.2) 10.23 (-2.44, 2.30) 10.33 (-2.44, 2.30) 13.30 (-2.34, 7.30, 7.4) 13.30 (-2.34, 7.30, 7.4) 13.32 (-2.34, 7.30, 7.2) 13.32 (-1.44, 6.21, 80) 7.29 (1.09, 13.49) 2.35 (1.30, 4.59) 5.11 (-5.32, 16.14) 6.67 (10.3, 12.31) -2.00 (-2.61, 5.2, 21.5)	Mean Difference
2.12.10.4MGT Datick Mysgaw2023 Dong Sila L2021 Hindi Watanabe 2014 Hindi Watanabe 2014 Hindi Watanabe 2019 Nagiro Tanaka 2019 Nagiro Tanaka 2019 Nagiro Tanaka 2019 Nagiro Tanaka 2019 List for overall effect 2 2.12.2 TARAT Data Husenan0007 Data Hyouk Bang2010 Joseph Hider 2009 Michael D. Lewek 2019 Historage D. Lewek 2019 Historage D. Lewek 2019 Test for overall effect 2 =	Expe Mean 13.5 20.41 22.3 26.9 2.5 4.14 00; Chi [#] = 2.30 (P 7.38 5.39 2.75 5.39 2.75 5.39 2.75 5.39 0.01; Chi [#] = 0.08 (P	talent so so so so so so so so so so	al <u>Total</u> 17 17 11 12 14 21 106 6 (P 166 9 27 62 33 3 9 156 df = 5 262	(<u>Mean</u> 6.7 10.18 19.7 23.6 13.04 2.85 0.32 = 0.96); 11.78 2.46 -2.36 9.9 13.7 2 (P < 0.0	Control SD 15.92 20 33.3 33.05 24.37 34.39 33.01 1.85 5.71 1.85 5.71 1.96 5.71 1.96 6 26.51 00001); 1	Total 18 15 11 12 12 20 100 14 9 27 61 30 8 149 919 249	Weight 9.1% 5.9% 2.2% 2.4% 2.5% 4.0% 3.5% 31.6% 14.3% 15.4% 8.2% 12.7% 14.8% 2.9% 68.4% 6	Mean Difference IV , Random, 95% CI. 6.801-3.02, 16.62 10.2312.44, 23.01 3.3012.437, 30.47 3.3012.347, 30.47 3.301347, 25.08, 27.07 3.821+4.16, 21.801 7.291(1.09, 13.49) 3.821+4.16, 21.801 7.291(1.09, 13.49) 5.1115.522, 16.14 6.871(1.03, 12.31) 6.871(1.03, 12.31) 4.2014, 5.2121 -0.2445.539, 5.511	Mean Difforence N. Randem 95% CI
2.12.10.4RdGT Daticki Mysgaw2023 Dong Xiba L2021 Hiroki Wistanabe 2014 Hiroki Wistanabe 2014 Hiroki Wistanabe 2014 Hiroki Qattanabe 2016 Hiroki Qattanabe 2016 Hiroki Qattanabe 2016 Hiroki Qattanabe 2016 Hiroki Qattanabe 2016 Date Xiba Qattanabe 2016 Hiroki Qattanabe 2	Expe Mean 13.55 20.411 22.3 28.28 2.5 4.14 00; ChI [≠] = 2.30 (P 7.38 5.39 2.75 16.57 5.55 0 1.01; ChI [≠] 0.08 (P 1.01; ChI [≠] 0.08 (P 1.01; ChI [≠] 0.08 (P 1.01; ChI [≠] 0.08 (P 1.01; ChI ⁺ 0.08 (P)	str 13.88 34.67 34.67 34.67 34.67 34.67 34.67 34.67 34.67 34.67 34.67 34.67 34.67 34.67 34.67 5.67 26.68 15.98 5.34 24.95 25.722, 26.367, 27.22, 26.367,	al <u>Total</u> 17 17 11 12 14 21 106 6 (P 166 9 27 62 33 3 9 156 df = 5 262	(<u>Mean</u> 6.7 10.18 19.7 23.6 13.04 2.85 0.32 = 0.96); 11.78 2.46 -2.36 9.9 13.7 2 (P < 0.0	Control SD 15.92 20 33.3 33.05 24.37 34.39 33.01 1.85 5.71 1.85 5.71 1.96 5.71 1.96 6 26.51 00001); 1	Total 18 15 11 12 12 20 100 14 9 27 61 30 8 149 919 249	Weight 9.1% 5.9% 2.2% 2.4% 2.5% 4.0% 3.5% 31.6% 14.3% 15.4% 8.2% 12.7% 14.8% 2.9% 68.4% 6	Mean Difference IV , Random, 95% CI. 6.801-3.02, 16.62 10.2312.44, 23.01 3.3012.437, 30.47 3.3012.347, 30.47 3.301347, 25.08, 27.07 3.821+4.16, 21.801 7.291(1.09, 13.49) 3.821+4.16, 21.801 7.291(1.09, 13.49) 5.1115.522, 16.14 6.871(1.03, 12.31) 6.871(1.03, 12.31) 4.2014, 5.2121 -0.2445.539, 5.511	Mean Difference M. Bandem, 35% CI ++++++++++++++++++++++++++++++++++++
2.12.10.4MGT Dahich Myagaw2023 Dong Xia L2021 Hinoki Watanake 2014 Hinoki Watanake 2014 Hinoki Watanake 2014 Hinoki Watanake 2015 Nagino Tanake 2019 Subtotat (9%) C0 Heterogeneh; Tau*a 20 Subtotat (9%) C0 Heterogeneh; Tau*a 20 Joseph Hidler 2009 Michael D. Lewek 2015 Subtotat (9%) C0 Heterogeneh; Tau*a 20 Heterogeneh; Tau*a 20 Heterogeneh; Tau*a 20	Exqu Mean 13.5 20.41 22.3 26.9 28.28 2.5 4.14 00; ChI [#] 2.30 (P 7.38 5.39 2.75 16.57 0 0.00; ChI [#] 0.008 (P 0.008 (P	erimentit 30 13.68 34.67 34.65 24.98 =1.49, df 15.98 5.3 24 = 0.02) 4.05 1.67 25.68 5.3 24 = 0.02) ************************************	al <u>Total</u> 17 17 11 12 106 9 27 62 33 9 156 df = 5 2622 df = 1:	(<u>Mean</u> 6.7 10.18 19.7 23.6 0.32 0	Control SD 15.92 200 33.3 33.05 24.37 33.01 1.85 13.96 15.92 6 26.51 13.96 00001); I 000001); I	Total 18 15 11 12 12 12 12 20 100 100 14 9 27 61 30 8 149 919 249 β [#] = 919 249	Weight 9.1% 5.9% 2.2% 2.4% 2.5% 4.0% 3.5% 31.6% 14.3% 15.4% 8.2% 12.7% 14.8% 2.9% 68.4% 6	Mean Difference IV , Random, 95% CI. 6.801-3.02, 16.62 10.2312.44, 23.01 3.3012.437, 30.47 3.3012.347, 30.47 3.301347, 25.08, 27.07 3.821+4.16, 21.801 7.291(1.09, 13.49) 3.821+4.16, 21.801 7.291(1.09, 13.49) 5.1115.522, 16.14 6.871(1.03, 12.31) 6.871(1.03, 12.31) 4.2014, 5.2121 -0.2445.539, 5.511	Mean Difforence N. Randem 95% CI

Figure 3.—Forest plots for the analysis of walking speed, cadence and their subgroups.

indicated that there was a statistical difference between the experimental group and the control group (SMD=-0.55, 95% CI: -0.99, -0.12; P=0.01).

Functional Ambulation Categories (FAC)

Sixteen studies were included, involving 768 patients with lower limb dysfunction after stroke. Due to the heterogeneity test results (P<0.00001, I²=87%), a random effect model analysis was used. And as shown in Figure 7C, the results indicated that there was a statistical difference between the experimental group and the control group (SMD=0.32, 95% CI: 0.01, 0.63; P=0.04).

Subgroup analysis of stroke onset time indicated that acute phase (SMD=0.32, 95% CI: -0.02, 0.66; P=0.07) showed a higher effect size than subacute or chronic phase (SMD=0.32, 95% CI: -0.13, 0.78; P=0.16), as shown in Figure 7C.

Angle of joint motion

It can be categorized into three aspects: affected hip, affected knee and affected ankle.

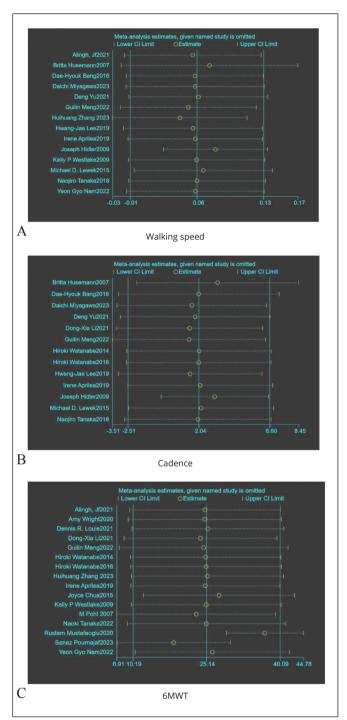


Figure 4.—Summary of sensitivity analysis plots.

In terms of changes in the affected hip motion, four studies were included, involving 200 patients with lower limb dysfunction after stroke. Due to the heterogeneity

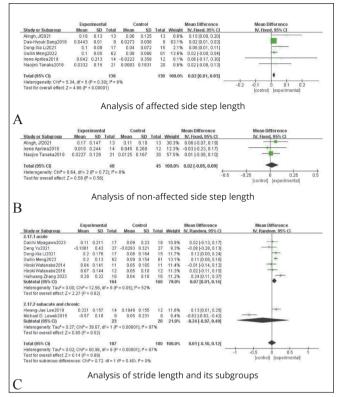


Figure 5.—Forest plots for the analysis of affected side step length, nonaffected side step length, stride length and their subgroups.

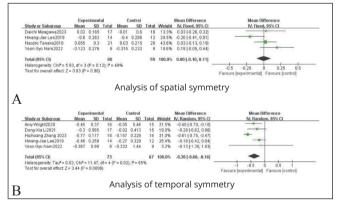


Figure 6.—Forest plots for the analysis of symmetry.

test results (P=0.24, I²=29%), a fixed effect model analysis was used. And as shown in Figure 8A, the results indicated that there was no statistical difference between the experimental group and the control group (SMD=0.34; 95% CI: -1.62, 2.29; P=0.74).

In terms of changes in the affected knee motion, four studies were included, involving 200 patients with lower limb

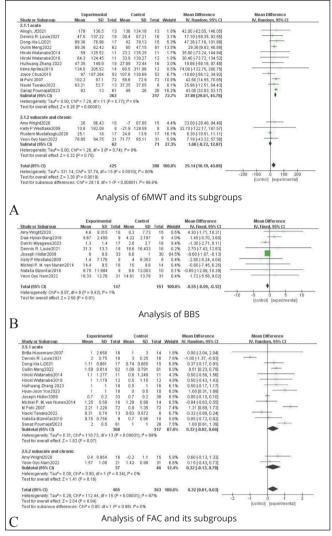


Figure 7.—Forest plots for the analysis of 6MWT, BBS, FAC and their subgroups.

dysfunction after stroke. Due to the heterogeneity test results (P=0.63, $I^2=0\%$), a fixed effect model analysis was used. And as shown in Figure 8B, the results indicated that there was no statistical difference between the experimental group and the control group (SMD=5.53, 95% CI: -1.69, 12.75; P=0.13).

In terms of changes in the affected ankle motion, four studies were included, involving 200 patients with lower limb dysfunction after stroke. Due to the heterogeneity test results (P=0.95, I²=0%), a fixed effect model analysis was used. And as shown in Figure 8C, the results indicated that there was no statistical difference between the experimental group and the control group (SMD=1.23, 95% CI: -0.50, 2.95; P=0.16).

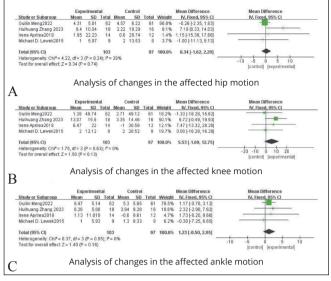


Figure 8.—Forest plots for the analysis of changes in the angle of joint motion.

Stride length

Nine studies were included, including 367 patients with lower limb dysfunction after stroke. Due to the heterogeneity test results (P<0.00001, I²=87%), a random effect model analysis was used. And as shown in Figure 5C, the results indicated that there was no statistical difference between the experimental group and the control group (SMD=0.01, 95% CI: -0.10, 0.12; P=0.89).

Subgroup analysis of stroke onset time reflected that acute phase (SMD=0.07, 95% CI: 0.01, 0.14; P=0.02) showed a better effect size than subacute or chronic phase (SMD=-0.24, 95% CI: -0.97, 0.49; P=0.52), as shown in Figure 5C.

Publication bias

Most of the included studies used walking speed and 6MWT as outcome indicators. Furthermore, funnel plots (Figure 9) showed that there was less publication bias in both of them.

Discussion

To investigate the specific effects of RAGT, researchers in randomized controlled trials compared O-RAGT or T-RAGT with CGT. Although RAGT requires less involvement from therapists, physicians, etc., it may be an improvement over traditional therapy. Our study found that most of the results were robust except for the three stud-

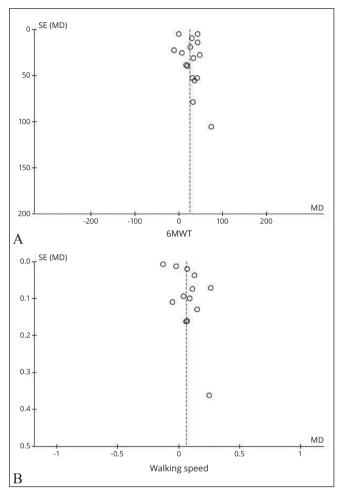


Figure 9.-Funnel plots.

ies^{27, 43, 49} involved in two indicators, cadence and 6MWT. Random allocation and allocation concealment emerged high risk or unclear may be the main reasons for the unrobust merger results. In addition, our study showed that RAGT was associated with the changes of the affected side step length, temporal symmetry, 6MWT and FAC which had potential clinical benefits for patients. But compared with the control group, the experimental group had no significant advantages in walking speed, cadence, spatial symmetry, balance, angle of joint motion changes and stride length. RAGT for post-stroke walking dysfunction is a growing area of research, with about 60% of the studies in this study published in 2018 or later.

Although the studies included in this review used slightly different instruments to measure physical function, they all included walking speed in their measurements. Walking speed, a prognosticator of survival and disability in the elderly, was associated with a 12% lower risk of death for every 0.1 m/s increase over at least five years of follow-up. However, this study found that RAGT and non-RAGT had similar improvements in speed which seems surprising. Although there is no obvious correlation between RAGT and speed, most studies^{36, 52-54} believe that RAGT has a positive effect on the improvement of step speed. Tedla et al.55 reported that there was no significant difference between RAGT and CGT on speed improvement, which is consistent with the results of another meta-analysis¹⁰ and ours. Moreover, the results of our meta-analysis indicated that the experimental group and the control group had similar improvements in cadence. Nevertheless, its change does not directly and accurately reflect the improvement of motion patterns. Thus, it can be better understood by combining and considering the results of changes in other indicators.

Compared with speed and cadence, symmetry can better reflect the degree of injury, compensatory mechanism and recovery of stroke patients.56 It has been noted that RAGT has greater improvement in temporal and spatial parameters than CGT.33, 57 However, few studies have shown a significant association between RAGT and improvements in motor symmetry. Our results extend this evidence by showing that RAGT improves temporal symmetry but not spatial symmetry. Heidi *et al.*¹⁰ came to a similar conclusion in this regard. As the operating mode of RAGT is to set movement parameters in advance, patients may obtain a better physiological movement pattern that is closer to normal. Furthermore, self-driven training and training with properly afferent feedback can stimulate changes in motor cortex excitability.58 Thus more stable and rhythmic peripheral input may be the main reason for the improvement of temporal symmetry. And RAGT may promote the output of central motor control through the input of peripheral stimuli that mimic physiological gait patterns. Besides, intensive and repetitive assisted walking in coordination with voluntary motion may enhance motor relearning through neuroplasticity.

Spatial symmetry has more stringent requirements on balance, muscle strength, motor control and other aspects. Therefore, it is perhaps not surprising that RAGT does not show a significant correlation with it. Additionally, there was a significant difference in the improvement of affected side step length while there was not in the improvement of non-affected side step length. This suggests that the contribution of step length to spatial symmetry may be limited. And the changes in the improvement of the angle of joint motion were not significantly different between groups, which seems to confirm the limitations of RAGT in improving spatial symmetry. Yet, the limited sample size and the inconsistent quality of the evidence (including 1 medium-quality study⁴⁰ and 3 high-quality studies^{25, 30, 50}) impacted the stringency of the conclusion. Moreover, joint motion requires the cooperation of peripheral sensation, central control, muscle function and other aspects. Strong muscle function supports strong joint movement. In other words, muscle function may take precedence over joint performance. Therefore, it is necessary to further explore the relationship between muscle function and spatial symmetry. That is to explore the interaction between dynamics and kinematics. Notably, electromyography is a reliable approach.

A good endurance level plays a prominent role in improving walking ability after stroke. 6MWT is an important test to assess walking endurance which reflects functional compensatory ability for daily physical activity.59,60 And few studies have focused on the endurance improvement of stroke patients by RAGT. Delightfully our study noticed this and indicated that RAGT had a better performance in improving endurance than the control group. Compared to CGT, RAGT can provide safer (with BWS) and higher-intensity (reaching running speed) training to promote the cardiorespiratory function of patients. Also, in this meta-analysis, RAGT significantly improved the FAC score, suggesting that it has advantages in enhancing the ability to walk on the ground and stairs independently. This finding is consistent with the results of a randomized controlled trial by Yeung et al.,⁶¹ which found that RAGT can reduce functional gait dependence and promote motor recovery. The ability of stroke patients to walk independently in the community was associated with increased walking speed.⁶² Although our study found no statistical difference in speed, its effect size is still worthy of recognition.

In summary, we confirmed that RAGT has positive effect on walking dysfunction after stroke. Proprioceptive input plays an important role in neuroplasticity. The interaction of proprioception, superficial senses and multisensory afferents on neuroplasticity could be the focus of further study.

Robot training type

Subgroup analysis revealed that O-RAGT had a better effect size than T-RAGT in terms of speed improvement. Compared to T-RAGT, which is attached to a fixed exoskeleton, O-RAGT has no restrictions on treadmill and allows walking training to be complete in a more realistic environment.¹⁶ Hence, patients treated with O-RAGT may exhibit greater autonomy of motivation. At the same time, due to the absence of BWS, O-RAGT may provide a stronger pressure sensation from the mechanoreceptors under foot soles than T-RAGT. Additionally, stronger sensory feedback is beneficial to stimulate plastic changes in gait patterns.⁶³ Only when proprioceptive feedback was provided, cortical-muscular coherence increased with a predominant information flow from the sensorimotor cortex to the muscles.⁶⁴ Thus future studies focused on exploring the impacts of different RAGTs on gait patterns could enhance the understanding of neuroplasticity. Moreover, the use of NIR and EEG may be able to contribute to this understanding.

In terms of cadence, subgroup analysis revealed a significantly better effect size in the O-RAGT group than T-RAGT. This finding corroborates that patients in the O-RAGT group may demonstrated a stronger self-drive in treatment. Yet, for FAC enhancement, the effect size was slightly better in the T-RAGT group. Only two^{31, 49} of the included studies in the O-RAGT group utilized BWS whereas all of the studies included in the T-RAGT group used BWS. And BWS can facilitate easier implementation of RAGT for patients with poorer functional status. And there is also more room for the improvement of functional independence among them. Consequently, it makes sense to have such a change.

Post-stroke time

After subgroup analysis, the heterogeneity decreased significantly, indicating that stroke onset time is probably the source of heterogeneity in 6MWT. Meanwhile, there exists a statistical difference between subgroups. The improvement of endurance was better in the acute stage than in the non-acute stage. In fact, the first six months of stroke are considered the golden period of treatment, so the superiority of functional improvement during this period is naturally self-evident. Although FAC and stride length did not have a statistical difference between subgroups, the differences in effect size could also reflect the superiority of early recovery from stroke to some extent.

Strengths of the study

One of the strengths of this study lies in the extensive database search that was conducted. This methodology not only amplifies the comprehensiveness of the review but also augments the likelihood of identifying a diverse range of studies, thereby offering a more holistic view of the current research landscape. Furthermore, this meta-study confirms the efficacy of RAGT in the treatment of walking dysfunction after stroke and supplements the literature on the effects of RAGT on kinematic parameters. Also, to our knowledge, this study fills the gap of differences in efficacy between different RAGTs. This effort could potentially foster a deeper understanding and facilitate advancements in the treatment of RAGT, providing a theoretical foundation for further research and discussions in this field, as well as informing clinical decision-making.

Limitations of the study

The main limitation of this study is the lack of a metaanalysis of different RAGT treatment protocols and systems. The operation of some RAGT systems like HAL requires specially trained personnel. Although instrumental measurements largely make the results more objective, differences in protocols and systems are still inconsistent factors that may give rise to some heterogeneity. Additionally, some studies may cause potential bias due to the difficulty of implementing blind methods. It inevitably casts a shadow on the overall findings. While this does not invalidate our results, it does necessitate a more cautious and discerning interpretation.

Conclusions

According to the available data, RAGT plays a role in the improvement of walking dysfunction after stroke. Also, RAGT does perform better in some kinematic indexes compared with non-RAGT training. O-RAGT may be superior to T-RAGT. However, whether it is superior to CGT needs to be demonstrated in further studies. These conclusions should be viewed with caution in light of the recognized shortcomings of the existing studies. Further large-scale multi-center studies are urgently needed which compare different treatment regimens and RAGT devices.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Shishi Chen conceived the manuscript and analyzed the data. Dingyu Wang and Wanying Zhang searched the literature and collected data. Shishi Chen, Wanying Zhang and Zhaoming Chen assessed methodological quality and contributed to data curation and writing of the first draft. Shishi Chen and Zhaoming Chen participated in verification, writing, review and editing. All authors contributed to the article and approved the final manuscript. *History*

Article first published online: April 22, 2024. - Manuscript accepted: April 9, 2024. - Manuscript revised: February 28, 2024. - Manuscript received: November 27, 2023.

Supplementary data

For supplementary materials, please see the HTML version of this article at www.minervamedica.it

Authors' contributions