

Constraint-induced movement therapy in treatment of acute and sub-acute stroke: a meta-analysis of 16 randomized controlled trials

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Abstract

OBJECTIVE: The aim of this meta-analysis was to evaluate the clinical efficacy of constraint-induced movement therapy in acute and sub-acute stroke.

DATA SOURCES: The key words were stroke, cerebrovascular accident, constraint-induced therapy, forced use, and randomized controlled trial. The databases, including China National Knowledge Infrastructure, WanFang, Weipu Information Resources System, Chinese Biomedical Literature Database, PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, were searched for studies on randomized controlled trials for treating acute or sub-acute stroke published before March 2016.

DATA SELECTION: We retrieved relevant randomized controlled trials that compared constraint-induced movement therapy in treatment of acute or sub-acute stroke with traditional rehabilitation therapy (traditional occupational therapy). Patients were older than 18 years, had disease courses less than 6 months, and were evaluated with at least one upper extremity function scale. Study quality was evaluated, and data that met the criteria were extracted. Stata 11.0 software was used for the meta-analysis.

OUTCOME MEASURES: Fugl-Meyer motor assessment of the arm, the action research-arm test, a motor activity log for amount of use and quality of movement, the Wolf motor function test, and a modified Barthel index.

RESULTS: A total of 16 prospective randomized controlled trials (379 patients in the constraint-induced movement-therapy group and 359 in the control group) met inclusion criteria. Analysis showed significant mean differences in favor of constraint-induced movement therapy for the Fugl-Meyer motor assessment of the arm (weighted mean difference (WMD) = 10.822; 95% confidence intervals (95% CI): 7.419–14.226), the action research-arm test (WMD = 10.718; 95% CI: 5.704–15.733), the motor activity log for amount of use and quality of movement (WMD = 0.812; 95% CI: 0.331–1.293) and the modified Barthel index (WMD = 10.706; 95% CI: 4.417–16.966).

CONCLUSION: Constraint-induced movement therapy may be more beneficial than traditional rehabilitation therapy for improving upper limb function after acute or sub-acute stroke.

Key Words: nerve regeneration; stroke; constraint-induced movement therapy; meta-analysis; upper extremity function; rehabilitation; intensity; neural regeneration

Introduction

Stroke is a leading cause of disability, primarily resulting from motor impairment (Dobkin, 2005; Towfighi and Saver, 2011; Corbetta et al., 2015). Although most patients show large improvement in motor function soon after stroke, 75% of patients continue to have upper extremity deficits 3–6 months later (Pang et al., 2006; Ng et al., 2007; Chen et al., 2017).

Constraint-induced movement therapy (CIMT) is a neurorehabilitatory approach developed by Taub et al. (1993) that is characterized by restraint of the less affected upper limb and forced use of the affected arm. This is usually achieved by placing the less affected arm in a padded mitten and then engaging in extensive task-oriented training of the

affected arm for up to 90% of daily waking hours, 2 weeks per month (14 days in total) (Taub and Wolf, 1997; Kwakkel et al., 2015). However, receiving intensive occupational therapy for 6 hours every day leads to a low level of treatment compliance. To overcome this difficulty, a modified CIMT (mCIMT) has been developed in last few decades (Page et al., 2001, 2002; Wang et al., 2011; Taub et al., 2013; Souza et al., 2015; Zhu et al., 2016). The mCIMT is characterized by lower intensity training compared with traditional CIMT.

An increasing number of studies have demonstrated that CIMT after stroke, especially in the chronic phase (> 6 months), is more effective than standard rehabilitation measures (van der Lee et al., 1999; Wolf et al., 2006; Sterr et al., 2014; Park et al., 2015; Takebayashi et al., 2015; Ballester

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et al., 2016). However, whether CIMT has higher efficacy than conventional rehabilitation in acute or sub-acute stroke remains a key question. Some studies have shown that CIMT is not suitable for rehabilitation in patients with acute stroke. High-intensity CIMT started in the first days and weeks post stroke may aggravate limb function deterioration (Dromerick et al., 2009). Additionally, animal experiments have proved that immediate casting of the unaffected forelimb may cause lesion enlargement that is presumed excitotoxic and is associated with a decrement in motor recovery (Kozlowski et al., 1996; Humm et al., 1999; DeBow et al., 2004; Diederich et al., 2012). However, some studies have indicated that CIMT interventions during the acute phase have a positive effect on upper limb motor function (Thrane et al., 2015). Nevertheless, a systematic evaluation of these studies is required to accurately understand the efficacy of CIMT.

Some systematic reviews have focused on the effects of mCIMT on upper limb motor function in patients with chronic stroke (Bonaiuti et al., 2007; Shi et al., 2011; Peurala et al., 2012; Janssen et al., 2013). To the best of our knowledge, only one systematic review has focused on CIMT/mCIMT in acute or sub-acute stroke (Nijland et al., 2011). However, these results were based on only five studies. Even fewer articles were included in the calculation of a single index, which had an inevitable negative impact on the reliability of the results. Further studies with larger sample sizes have been conducted since 2011 when the original review was published; therefore, a new systematic review is essential.

The purpose of this meta-analysis was to explore the effects of mCIMT on upper extremity motor function in patients with acute or sub-acute stroke. The results are based on an evaluation of CIMT efficacy for arm motor function and assessments of behavioral techniques, hours of training, and the time from stroke occurrence to trial enrollment.

Methods

Literature and search strategy

Potentially relevant literature was identified through computerized and manual searches. A number of publications were searched using MeSH terms and free words. The databases from which articles were sourced included China National Knowledge Infrastructure, WanFang, Weipu Information Resources System, Chinese Biomedical Literature Database, PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. The review period extended from the inception of each database to March 2016. The key words were stroke, cerebrovascular accident, constraint-induced therapy, forced use, and clinical trial. The language search was limited to English and Chinese. The following MeSH headings and key words were used: stroke, cerebrovascular accident, constraint-induced therapy, forced use, and randomized controlled trial. Additional relevant articles not captured by these databases were identified by reviewing references listed in the retrieved articles. This paper was prepared in accordance with the "Preferred Reporting Items for Systematic Reviews and

Meta-Analyses" (PRISMA) guidelines.

Study selection

Studies published before March 2016 were included if they met the following inclusion criteria: (1) a randomized clinical trial that included adult patients (≥ 18 years); (2) a CIMT/mCIMT group and a control group that received traditional rehabilitation therapy; (3) at least one of the following assessment methods: Fugl-Meyer motor assessment of the arm (FMA), the action research-arm test (ARAT), a motor activity log (MAL) for amount of use (AOU) and quality of movement (QOM), the Wolf motor function test (WMFT), or a modified Barthel index (mBI); (4) participants were in the acute or sub-acute phase after having a stroke (< 6 months); (5) published in English or Chinese.

Exclusion criteria: Patients meeting any of the following criteria were excluded (1) other rehabilitation therapies. This was to more specifically assess the specific effects of CIMT; (2) non-randomized trials.

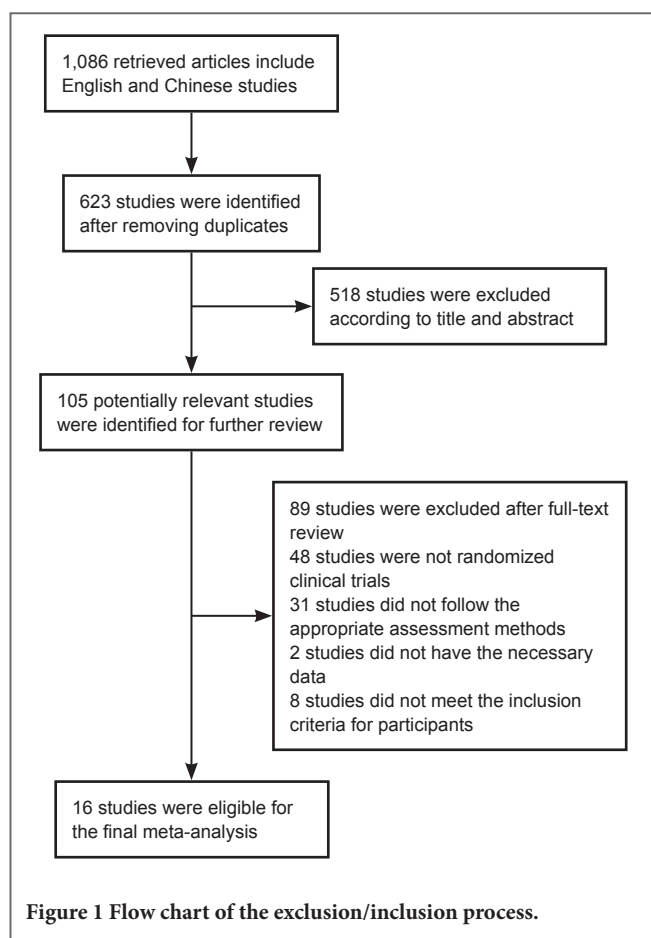
Two authors (Xi-hua Liu and Juan Huai) assessed the identified articles by reading titles and abstracts, to confirm that they satisfied the inclusion criteria. When a study did not contain sufficient information in the abstract to make a decision, the full text was reviewed. In the event of disagreement, a third reviewer (Shou-wei Yue) was consulted.

Quality assessment

Study quality of each article was assessed using the Physiotherapy Evidence Database (PEDro) scale (Maher et al., 2003) independently from each other. PEDro is a valid scale consisting of 11 items. One point was given for each criterion that was satisfied, with a maximum score of 10. A study scoring 4 or higher was considered to be high quality (Maher et al., 2003; Van Peppen et al., 2004). In the event of disagreement, a third reviewer (Shou-wei Yue) was consulted.

Statistical analysis

For each outcome variable, the results were pooled by calculating the weighted mean difference (WMD) and 95% confidence intervals (95% CI) when the outcomes were reported on the same scale. The WMD and the corresponding standard deviation were calculated using the difference in the post-intervention means between the experimental and control groups. The Q test was administered to test for between-study homogeneity, which was set at a significance level of 10%. A random effects model was used to calculate the pooled outcome variables if significant heterogeneity was found ($I^2 \geq 50\%$). For $I^2 < 50\%$, a fixed-effect model was used. Subgroup analyses were further conducted according to the degree of mCIMT, which deemed high-intensity (HI) or low-intensity (LO) according to the VECTORS study (Dromerick et al., 2009). Sensitivity analysis was also performed to assess the stability of the results. Publication bias was assessed using Begg's test and Egger's test, which were set at a significance level of 5%. Statistical analyses were conducted using STATA version 11 (StataCorp LP, College Station, TX, USA).



Results

Data retrieval

As shown in **Figure 1**, 1,086 potentially relevant studies were identified according to the literature search strategy. Of these, 623 were identified after removing duplicates. Subsequently, 518 studies were excluded based on the title and abstract. Of the remaining 105 studies, 89 were excluded after full-text review for varying reasons. For example, one paper was excluded because it did not provide sufficient data in the calculations (Brunner et al., 2012), while another was excluded because the patients in the control group received bimanual training rather than traditional rehabilitation therapy (Batool et al., 2015). Thus 16 prospective studies comprising 738 participants were included in the meta-analysis (Dromerick et al., 2000, 2009; Page et al., 2005; Ro et al., 2006; Boake et al., 2007; He et al., 2010; Wu et al., 2010; Zhang et al., 2011, 2015a; Singh and Pradhan, 2013; Huang et al., 2014; Yoon et al., 2014; El-Helow et al., 2015; Thrane et al., 2015; Liu et al., 2016; Song et al., 2016).

Characteristics of the studies

Of the 16 studies included in the final meta-analysis, 10 were written in English and 6 were in Chinese (**Table 1**). The effects of CIMT/mCIMT were evaluated in 5 studies using the ARAT, 6 using an mBI, 13 using the FMA, 4 using an MAL

(AOU and QOU), and 2 using the WMFT.

Quality assessment

Table 2 shows the quality assessment scores for the included studies, according to the PEDro scale. The PEDro scores ranged from 5 to 8 points, with a median score of 6.5 points. No study was excluded from further analysis.

Meta-analysis results

ARAT

Five studies (Dromerick et al., 2000, 2009; Page et al., 2005; Zhang et al., 2011; El-Helow et al., 2015) assessed CIMT/mCIMT efficacy using the ARAT. **Figure 2A** and **Table 3** show a significantly heterogeneous *WMD* (*WMD* [random]: 8.35; 95% *CI*: 1.98–14.71; *Z* = 4.19; *P* = 0.001; *I*² = 94.1%).

The two studies (Dromerick et al., 2009; Zhang et al., 2011) that used HI CIMT yielded a nonsignificant difference in favor of the control group (*WMD* [random]: 2.02; 95% *CI*: -7.18–11.23; *P* = 0.667). The four studies (Dromerick et al., 2000; Page et al., 2005; Dromerick et al., 2009; El-Helow et al., 2015) that used LO CIMT yielded a significant *WMD* in favor of the experimental group (*WMD*: 11.49; 95% *CI*: 5.61–17.37; *P* < 0.001).

mBI

Six studies (Dromerick et al., 2000; He et al., 2010; Wu et al., 2010; Zhang et al., 2011, 2015b; Song et al., 2016) assessed the efficacy of CIMT/mCIMT on basic activities of daily living function using an mBI. **Figure 2B** and **Table 3** show a significantly heterogeneous total standardized mean difference (*SMD*) for the mBI (*SMD* [random]: 10.706; 95% *CI*: 4.417–16.966; *Z* = 3.34; *P* = 0.001; *I*² = 91.2%).

One study used HI CIMT (*SMD* [random]: 13.46; 95% *CI*: 4.29–22.63; *Z* = 2.88; *P* = 0.004) and four studies used LO CIMT (*SMD* [random]: 10.28; 95% *CI*: 3.38–17.18; *Z* = 2.92; *P* = 0.003). Both HI and LO CIMT yielded significantly better mBI values than the control group.

FMA

Thirteen studies (Page et al., 2005; Ro et al., 2006; Boake et al., 2007; He et al., 2010; Wu et al., 2010; Zhang et al., 2011, 2015b; Singh and Pradhan, 2013; Huang et al., 2014; Yoon et al., 2014; El-Helow et al., 2015; Thrane et al., 2015; Song et al., 2016) were evaluated to determine the effects of CIMT/mCIMT on motor impairment using the FMA. **Figure 2C** and **Table 3** show a significantly heterogeneous total *SMD* for the FMA (*WMD* [random] = 10.822; 95% *CI*: 7.419–14.226; *Z* = 6.23; *P* < 0.001; *I*² = 85.4%; **Figure 2C**).

The studies that used HI CIMT and LO CIMT yielded significant differences. The subtotal studies that used HI CIMT and LO CIMT also yielded significant differences. The subtotal *WMD* for HI CIMT studies (*WMD* [random] = 7.45; 95% *CI*: 3.03–11.87; *Z* = 3.31; *P* = 0.001; *I*² = 65.5%) was lower than the subtotal *WMD* for LO CIMT studies (*WMD* [random] = 12.74; 95% *CI*: 8.83–16.66; *Z* = 6.23; *P* < 0.001;

Table 1 Characteristics of the 16 included studies

Study	No. of CIMT/ mCIMT patients	No. of control groups	Recruitment period (time after stroke)	Extra intervention	Length of therapy (week)	Assessment times	Intervention intensity of therapy	Outcome measures
Dromerick et al. (2000)	11	9	4–14 d	Not mentioned	2 wk	0, 14 d	2 h/d, 5 d/wk	ARAT, FIM, mBI
Page et al. (2005)	5	5	2–9 d	Not mentioned	10 wk	0, 70 d	0.5 h/d, 3 d/wk	FMA, ARAT, MAL
Ro et al. (2006)	4	4	6–12 d	Not mentioned	2 wk	0, 14, 90 d	3 h/d, 6 d/wk	FMA, GPT, MAL
Boake et al. (2007)	9	7	5–19 d	Not mentioned	2 wk	0, 14, 90 d	3 h/d, 6 d/wk	FMA, GPT, MAL
Dromerick et al. (2009)	35	17	9.7 ± 4.6 d	Not mentioned	2 wk	0, 14, 90 d	2 h or 3 h/d, 5 d/wk	ARAT, FIM, SIS, WBFS, GDS
He et al. (2010)	35	35	2–3 d/10–14 d	The same drug treatment	4 wk	0, 4 wk	1 h/d, 5 d/wk	FMA, BI
Wu et al. (2010)	60	60	2–3 d	The same drug treatment	4 wk	0, 4 wk	1 h/d	FMA, BI
Zhang et al. (2011)	13	12	< 3 mon	Not mentioned	2 wk	0, 2 wk	4 h/d, 5 d/wk	ARAT, FMA, mBI
Singh et al. (2013)	20	20	2–4 wk	Not mentioned	2 wk	0, 2 wk	2 h/d, 5 d/wk	WMFT, FMA
Huang et al. (2014)	24	23	3–12 wk	None	2 wk	0, 2 wk, 6 mon	3 h/d, 5 d/wk	WMFT, FMA, MAL
Yoon et al. (2014)	9	9	< 6 wk	Not mentioned	2 wk	0, 2 wk	6 h/d, 5 d/wk	9-hole Pegboard test, grip strength, Brunnstrom stage, WMFT, FMA, k-MBI
EI-Helow et al. (2015)	30	30	< 2 wk	Not mentioned	2 wk	0, 14 d	2 h/d, 5 d/wk	FMA, ARAT
Thrane et al. (2015)	24	23	< 4 wk	Not mentioned	2 wk	0, 14 d 6 mon	3 h/d, 5 d/wk	WFMT, FMA, upper extremity
Zhang et al. (2015)	30	30	1–10 d	Not mentioned	2 wk	0, 2, 6, 16 wk	2 h/d, 5 d/wk	mBI, FMA
Liu (2016)	31	26	< 3 mon	Not mentioned	2 wk	0, 2, 4 wk	2 h/d, 5 d/wk	ARAT, FMA, Lawton, IADL, MAL
Song et al. (2016)	30	30	6–12 d	Not mentioned	30 d	0, 1 mon	40 min/d	FMA, mBI

CIMT: Constraint-induced movement therapy; mCIMT: modified constraint-induced movement therapy; FMA: Fugl-Meyer motor assessment of the arm; GPT: grooved pegboard test; FIM: functional independence measure; ARAT: action research-arm test; MAL: motor activity log; Lawton IADL: Lawton instrumental activities of daily living scale; WMFT: Wolf motor function test; SIS: stroke impact scale; WBFS: Wong-Baker faces scale; GDS: geriatric depression-15 scale; mBI: modified Barthel index; min: minutes; h: hour(s); d: days; wk: weeks; mon: months.

$I^2 = 83.6\%$; **Figure 2C**).

MAL

Four studies (Page et al., 2005; Ro et al., 2006; Boake et al., 2007; Huang et al., 2014) assessed the efficacy of CIMT/mCIMT using an MAL. **Figure 3** shows that the meta-analysis results yielded a non-significant heterogeneous *WMD* for AOU (*WMD* [random] = 1.014; 95% *CI*: (–0.114, 2.142); $Z = 1.76$; $P = 0.078$; $I^2 = 92.3\%$), but a significant difference for QOU (*WMD* [random] = 0.812; 95% *CI*: 0.331–1.293; $Z = 3.31$; $P = 0.001$; $I^2 = 56.7\%$).

The studies using HI or LO CIMT yielded significant differences in favor of the experimental group for AOU (*WMD*_{HI} [random] = 0.61, 95% *CI*: 0.20–1.01, $Z = 2.94$, $P = 0.003$; *WMD*_{LO} [random] = 2.18; 95% *CI*: 1.89–2.47; $Z = 3.31$; $P = 0.001$) and QOU (*WMD*_{HI} [random] = 0.55, 95% *CI*: 0.14–0.97, $Z = 2.64$, $P = 0.008$; *WMD*_{LO} [random] = 1.21; 95% *CI*: 0.93–1.49; $Z = 8.38$; $P < 0.001$).

WMFT

Two studies (Huang et al., 2014; Yoon et al., 2014) assessed the efficacy of CIMT/mCIMT using the WMFT. Pooling the results indicated a non-significant heterogeneous *WMD* (*WMD* [fixed] = 5.998; 95% *CI*: –1.862–13.858; $Z = 1.50$; $P = 0.135$; $I^2 = 18.2\%$; **Figure 3C** and **Table 3**).

Publication bias and sensitivity analyses

As shown in **Table 4**, all P -values from the Begg's test (0.34–1.00) and the Egger's test (0.075–0.488) were greater than 0.05, indicating that no publication bias was detected. Results of the sensitivity analyses were similar to those of the overall meta-analysis ($P > 0.05$).

Discussion

Analysis of efficacy

To the best of our knowledge, the present study represents the second systematic review to quantitatively investigate the

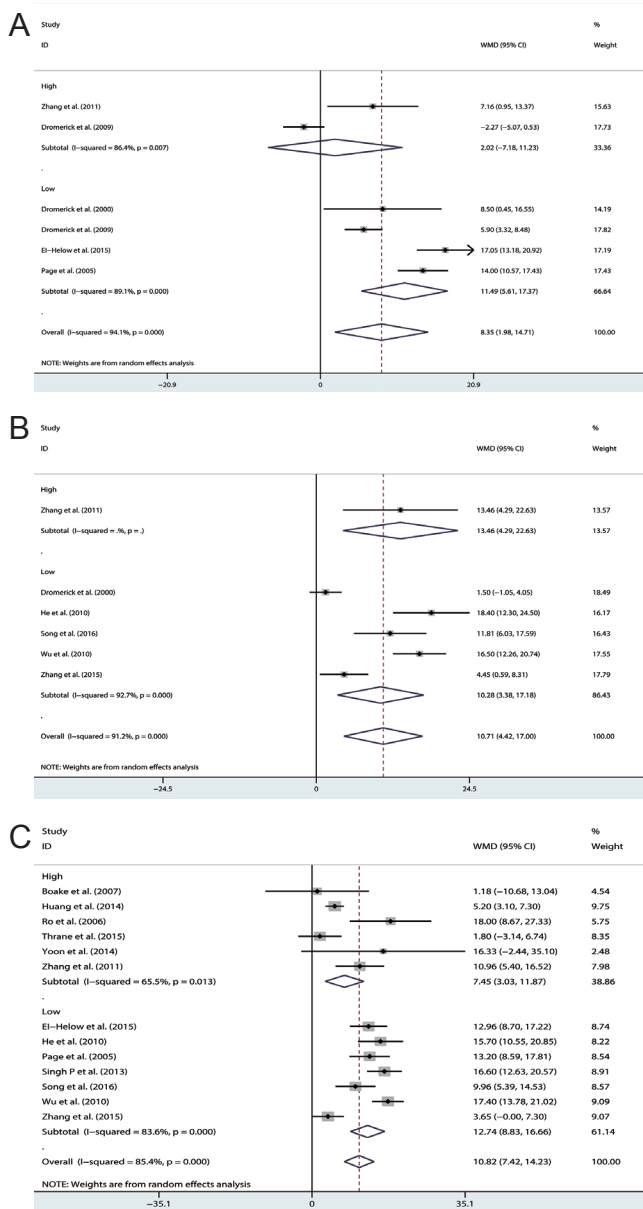


Figure 2 Effects of CIMT on the arm motor function of patients with acute or sub-acute stroke. Assessments included the ARAT (A), mBI (B), and FMA (C). CIMT: Constraint-induced movement therapy; ARAT: action research-arm test; mBI: modified Barthel index; FMA: Fugl-Meyer motor assessment of the arm.

clinical efficacy of CIMT in acute or sub-acute stroke. Compared with the first systematic review, we included more studies with larger sample sizes, which should strengthen the reliability of our conclusions. We found that CIMT or mCIMT may be more beneficial in acute or sub-acute stroke than traditional rehabilitation therapy. A total of 379 CIMT patients and 359 healthy controls were included in the meta-analysis, which greatly improved the statistical power and credibility of the conclusions over what was possible considering each study individually. The times for clinical outcome assessment differed among the studies. In our meta-analysis, we only compared the clinical outcomes after rehabilitation therapy to reduce any heterogeneity among the studies.

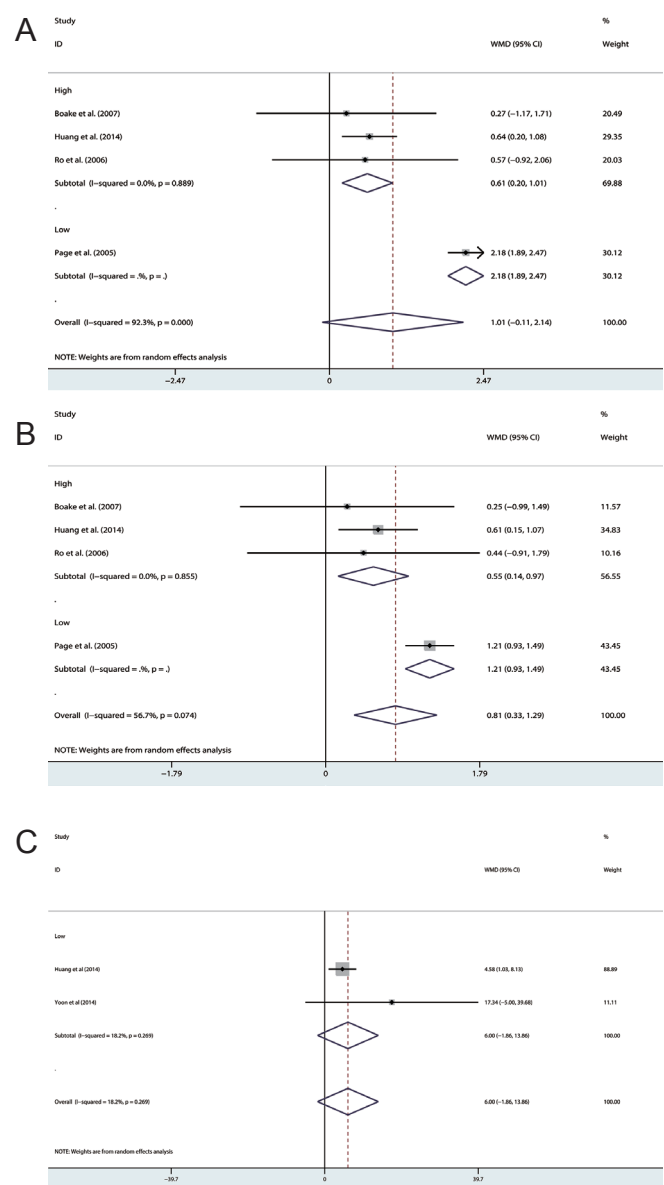


Figure 3 Effects of CIMT on arm motor function of patients with acute or sub-acute. Assessments include the AOU (A), QOM (B), and WMFT (C).

CIMT: Constraint-induced movement therapy; AOU: amount of use; QOM: quality of movement; WMFT: Wolf motor function test; WMD: weighted mean difference; 95% CI: 95% confidence intervals.

CIMT/mCIMT had significant effects on arm motor function and activities of daily living in acute and sub-acute stroke. However, no significant difference was found on the motor activity log-amount of use (MAL-AOU) or the WMFT. The results of subgroup analysis by CIMT degree also yielded significantly positive WMDs for most outcome measures compared with the control group. The I^2 values in both subgroups became smaller compared with the total value, which indicated that heterogeneity decreased among the included studies. This might suggest that the amount of CIMT training was one critical factor that affected the clinical results. Critically, the WMDs for LO CIMT were larger than those for HI CIMT, which suggests that LO CIMT may

Table 2 Methodological quality of the included studies - assessed with the 10-item Physiotherapy Evidence Database (PEDro) scale

Study	Eligibility criteria specified (Yes/No)	Random allocation	Concealed allocation	Comparable at baseline	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimates and variability	PEDro total score (0–10)
Dromerick et al. (2000)	Yes	1	0	1	0	0	1	1	0	1	1	6
Page et al. (2005)	Yes	1	1	1	0	0	1	1	1	1	1	8
Ro et al. (2006)	Yes	1	0	1	0	0	1	1	1	1	1	7
Boake et al. (2007)	Yes	1	0	1	0	0	1	0	1	1	1	6
Dromerick et al. (2009)	Yes	1	0	1	0	0	1	1	1	1	1	7
He et al. (2010)	Yes	1	0	1	0	0	1	1	1	1	1	7
Wu et al. (2010)	Yes	1	0	1	0	0	1	1	1	1	0	6
Zhang et al. (2011)	Yes	1	0	1	0	0	0	1	1	1	1	6
Singh et al. (2013)	Yes	1	0	1	0	0	1	1	1	1	1	7
Huang et al. (2014)	Yes	1	0	1	0	0	1	1	0	1	0	5
Yoon et al. (2014)	Yes	1	0	1	0	0	1	0	1	1	1	6
EI-Helow et al. (2015)	Yes	1	0	1	0	0	1	0	1	1	1	6
Thrane et al. (2015)	Yes	1	0	1	0	0	1	1	1	1	1	7
Zhang et al. (2015)	Yes	1	0	1	0	0	1	1	1	1	1	7
Liu (2016)	Yes	1	0	1	0	0	1	0	1	1	1	6
Song et al. (2016)	Yes	1	0	1	0	0	1	1	1	1	1	7

Table 3 Meta-analysis of constraint-induced movement therapy in acute and sub-acute stroke

	No. of studies	WMD	95% CI	Z	PZ	Statistical mode	I ² (%)	P
ARAT	5	8.35	1.98–14.71	4.19	0.001	Random	86.0	< 0.001
BI	6	10.706	4.417–16.966	3.34	0.001	Random	91.2	< 0.001
FMA	13	10.822	7.419–14.226	6.23	<0.001	Random	85.4	< 0.001
MAL-AOU	4	1.014	-0.114–2.142	1.76	0.078	Random	92.3	< 0.001
MAL-QOM	4	0.812	0.331–1.293	3.31	0.001	Random	56.7	0.074
WMFT	2	5.998	-1.862–13.858	1.50	0.135	Random	18.2	0.269

WMD: Weighted mean difference; 95% CI: 95% confidence intervals; ARAT: action research-arm test; mBI: modified Barthel index; FMA: Fugl-Meyer motor assessment of the arm; MAL-AOU: motor activity log - amount of use; MAL-QOM: motor activity log - quality of movement; WMFT: Wolf motor function test.

Table 4 Publication bias assessed by Begg’s test and Egger’s test (P)

Statistics	ARAT	BI	FMA	MAL-AOU	MAL-QOM	WMFT
Begg’s test	0.851	0.348	1.00	1.00	1.00	–
Egger’s test	0.732	0.082	0.282	0.075	0.203	–

ARAT: Action research-arm test; mBI: modified Barthel index; FMA: Fugl-Meyer motor assessment of the arm; MAL-AOU: motor activity log amount of use; MAL-QOM: motor activity log quality of movement; WMFT: Wolf motor function test.

be better than HI CIMT in acute and sub-acute stroke.

The biological mechanism underlying the efficacy of CIMT in acute and sub-acute stroke is still unclear (Zhao et al., 2009, 2013; Zhang et al., 2015b). Experimental studies have shown that hydrogel-delivered brain-derived neurotrophic factor promotes tissue repair and recovery after stroke (Cook et al., 2017). Our analysis showed that the results from the included studies differed from each other in some aspects. The main reason is likely the variable inclusion criteria. Patients in all studies were recruited at the acute or sub-acute phase (< 4 months) after stroke; however, this is still a relatively long period. The recruitment period in most of the studies was set at less than 2 weeks, while the recruitment period in the studies by Singh and Pradhan (2013) and Yoon et al. (2014) were greater than 2 weeks. Such differences in the inclusion criteria might have a substantial influence on the clinical effects. Another reason for the heterogeneity might be the variations in the intensity and duration of the intervention. For instance, the patients in most of the studies received 2 weeks of therapy for 2 or 3 hours per day, while in some studies, the patients received longer (4 or 10 weeks) or more intensive (4 or 6 hours per day) interventions. Inevitably, this also had a strong influence on the clinical effects.

Potential biases in the present study

Begg's test and Egger's test were used to explore the potential publication bias. Although no publication bias was detected, publication bias should also not be ignored because null results tend not to be published. Studies with large positive results are often much easier to publish than studies with negative results (Papageorgiou et al., 2015; Sedgwick, 2015). Therefore, we cannot rule out publication bias.

Limitations of the present meta-analysis

The present study has several limitations. First, we only compared the short-term efficacies of the interventions for the two groups. The long-term efficacy (more than 3 months) was not included because the data were limited, although its clinical significance holds greater value. Second, there was heterogeneity of results among the included studies even though the inclusion criteria were clearly defined in the present study. The recruitment period (days after stroke) and intensity of therapy differed across the studies, and this inevitably affected the reliability of the meta-analysis results.

Conclusion

In summary, the present meta-analysis demonstrated that CIMT or mCIMT might be more beneficial than traditional rehabilitation therapy in the acute and sub-acute stroke. Furthermore, LO CIMT may be better than HI CIMT. These findings might have clinical significance for the rehabilitation of patients within acute or sub-acute stroke. However, large-scale, well-designed multi-center studies are needed to further confirm the impact that degree of CIMT or mCIMT has on functional outcomes in acute and sub-acute stroke.

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Author contributions: XHL and SWY conceived the study and participated in the study design. XHL and JH did data collection. XHL and YZ accessed the risk of bias of references. JG performed statistical analysis. SWY participated in the design of the study and coordination. All authors approved the final version of the paper.

Conflicts of interest: None declared.

Data sharing statement: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Plagiarism check: Checked twice by iThenticate.

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