

Contralateral C7 Nerve Root Transfer for Function Recovery in Adults: A Meta-analysis

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Abstract

Background: Root avulsion to all 5 roots of the brachial plexus is a common presentation and keeps a major reconstructive challenge. The contralateral C7 (CC7) nerve transfer has been used in treating brachial plexus avulsion injury (BPAI) since 1986. However, the effectiveness of the procedure remains a subject of controversy. The aim of this meta-analysis was to study surgical outcomes regarding motor and sensory recovery after CC7 nerve transfer.

Methods: Chinese or English (i.e., “contralateral c-7”, “contralateral c7”, “c7 nerve root”, and “seventh cervical nerve root”) keywords were used for a literature search for articles related to CC7 nerve transfer in several databases (i.e., PubMed, Cochrane, Embase, CNKI, CQVIP, and Wanfang Data). Clinical research articles were screened, and animal studies as well as duplicate publications were excluded. Muscle strength and sensory recovery were considered to be effective only when the scores on the United Kingdom Medical Research Council scale were equal to or higher than M3 and S3, respectively.

Results: The overall ipsilateral recipient nerve recovery rates were as follows: the efficiency rate for muscle strength recovery after CC7 nerve transfer was 0.57 (95% confidence interval [CI]: 0.48–0.66) and for sensory recovery was 0.52 (95% CI: 0.46–0.58). When the recipient nerve was the median nerve, the efficiency rate for muscle strength recovery was 0.50 (95% CI: 0.39–0.61) and for sensory was 0.56 (95% CI: 0.50–0.63). When the recipient nerve was the musculocutaneous nerve and the radial nerve, the efficiency rate for muscle strength recovery was 0.74 (95% CI: 0.65–0.82) and 0.50 (95% CI: 0.31–0.70), respectively.

Conclusions: Transfer of CC7 nerves to musculocutaneous nerves leads to the best results. CC7 is a reliable donor nerve, which can be safely used for upper limb function reconstruction, especially for entirely BPAI. When modifying procedures, musculocutaneous nerves and median nerve can be combined as recipient nerves.

Key words: Contralateral C7; Functional Recovery; Meta-analysis; Nerve Transfer

INTRODUCTION

Brachial plexus avulsion injury (BPAI) represents one of the most devastating injuries of the upper extremity, and nerve transfer is the most frequently used method in restoring upper limb function for such serious lesion. Based on the development of microsurgical techniques with knowledge for microanatomy of peripheral nerve, various donors have been found, such as intra- or extra-plexus nerve donor, including accessory nerve transfer, intercostal nerve transfer, and phrenic nerve transfer. However, with the rapid growth of high-velocity traffic, there have been increasing high-energy accidents over the recent years which resulted in more extensive trauma. In these cases, even fewer donor nerves could be used for reinnervation. This prompts us to

seek more donor sources for brachial plexus reconstruction. Since the first contralateral C7 (CC7) nerve root transfer was performed in Shanghai Huashan Hospital in 1986 by Dr. Gu *et al.*,^[1] this donor nerve is widely used as a power nerve for nerve transfer in clinics for brachial plexus injury reconstruction, especially for entire brachial plexus root avulsion lesions. It was an innovative solution providing

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a substantial number of axons for motor and sensory restoration of the paralyzed upper limb without greatly compromising the function of the donor limb. So far, many studies have been conducted on the effects of CC7 nerve transfer on ipsilateral muscle strength and sensory recovery. However, the results of those studies are inconsistent, and there has been no systematic quantitative analysis. Based on the currently available literature, we conducted a meta-analysis of ipsilateral motor and sensory recovery in adults after CC7 nerve transfer. These meta-analysis results are expected to be used as a reference for selecting surgical approaches or designing therapeutic strategies for CC7 nerve transfer.

METHODS

Data sources

We conducted local and international literature searches using the following databases: PubMed, Cochrane, Embase, CBM, CNKI, CQVIP, and Wanfang Data. We conducted a comprehensive search and retrieved publications from 1986 to January 2016. Chinese keywords or English keywords (i.e., “contralateral c-7,” “contralateral c7,” “c7 nerve root,” and “seventh cervical nerve root”) were used. To comprehensively search for clinical research articles related to CC7 nerve transfer, we screened all abstracts from the publications we found, regardless of whether they were published in Chinese or English. When the abstract was ambiguous, we screened the full text. Two groups performed parallel screening, and if there was any objection, discussion will be needed to decide which will be included.

Inclusion and exclusion criteria

The inclusion criteria are as follows: (1) type of publication: original studies including prospective studies, retrospective studies, and bidirectional studies were included; (2) the study participants were patients subjected to CC7 nerve transfer; and (3) the publication reported objective performance indexes for ipsilateral exercise intensity or muscle strength or other indexes of sensory recovery.

The exclusion criteria are as follows: (1) the publication was a review article; (2) the publication involved animal experiments; (3) no CC7 nerve transfer was reported; (4) repeated study or repeated publication of the same trial; (5) the results were not clearly or precisely reported; (6) lack of extractable data; (7) the mean age of the study participants was under 18 years or the age of the study participants was not clearly reported; and (8) the publication was a case study.

Data extraction

Data extraction was performed by multiple evaluators. The demographic and descriptive data included the first author's name, publication year, location, sample size, sex, age, injury type, preoperative period (i.e., the time interval between injury and surgery), and follow-up time. The data also included various scores of muscles strength and sensory recovery. Data extraction was conducted based on a preset data-extraction form.

We conducted a quality assessment of each study using the Newcastle–Ottawa scale (NOS). NOS is widely used for assessing the quality of nonrandomized control trial publications. The maximum score is nine stars, and the publication is considered to be of acceptable quality if it achieves a score of more than six stars.

Statistical analysis

Using the extracted data, we performed an analysis of surgery outcomes based on the differences between recipient nerves. The Stata 12.0 software package (Stata Corp., College Station, TX, USA) was used to conduct the meta-analysis. We calculated total weighted mean differences (WMDs) and 95% confidence intervals (CIs). When the study results were homogeneous ($I^2 \leq 50\%$), we applied a fixed-effects model, otherwise a random-effects model. The WMD is applied to study the continuity variable which measurement unit is the same, and it can eliminate the effect of the absolute value on the results for the original measurement study and reflect the real experimental effects. Funnel plots are used to check for the existence of publication bias in this study. In the absence of publication bias, it assumes that studies with high precision will be plotted near the average; deviation from this shape can indicate publication bias.

RESULTS

The literature search retrieved a total of 327 publications, of which 120 were in Chinese and 207 were in English. After excluding publications that involved animal experiments or were published repeatedly, we evaluated the remaining publications by screening the abstracts and then the full text according to the inclusion and exclusion criteria. In total, we obtained 27 publications (10 in Chinese and 17 in English) that met the criteria for quantitative and synthetic analysis as shown in Figure 1. The included publications all had a relatively high NOS quality score. The basic characteristics and main conclusions of these publications are shown in Tables 1 and 2.

The recipient nerve of a CC7 nerve root could be a median nerve, radial nerve, musculocutaneous nerve, or triceps brachii nerve. To draw a more comprehensive conclusion, we analyzed the summarized results from all recipient nerves, and then conducted individual analyses of the median nerve, radial nerve, and musculocutaneous nerve, respectively, since these were the three nerves investigated in those studies with relatively large sample sizes. In accordance with the United Kingdom Medical Research Council (MRC) scale, muscle strength recovery and sensory recovery were considered to be effective only when the scores were equal to or greater than M3 and S3, respectively.

All recipient nerves

Muscle strength recovery efficiency rate

The total number of studies that assessed the strength of postoperative muscles was 27, and the pooled sample size was 694. Of these publications, five were excluded from the meta-analysis due to reports of an either 100% or 0% efficiency rate. Owing to the relatively low homogeneity

among these studies ($P < 0.001$, $I^2 = 82.8\%$), a random-effects model was employed here. The WMD was 0.57, and the 95% CI was 0.48–0.66. The overall efficiency rate of muscle strength recovery after CC7 nerve transfer was 0.57. The detailed results are shown in Figure 2a.

The results of the bias detection analysis are shown in Figure 2b. The relatively symmetrical plot indicates that the bias is relatively low.

Sensory recovery efficiency rate

The total number of studies assessing postoperative sensory recovery was 13, and the pooled sample size was 249. Owing to the relative homogeneity among these studies ($P < 0.001$, $I^2 = 42.7\%$), a fixed-effects model was employed here. The WMD was 0.52, and the 95% CI was 0.46–0.58. The overall sensory recovery efficiency rate after CC7 nerve transfer was 0.52. The detailed results are shown in Figure 3a.

The results of the bias detection analysis are shown in Figure 3b. The figure is relatively symmetrical, which indicates that the bias is relatively low.

Median nerve as recipient nerve Muscle strength recovery efficiency rate

The total number of studies assessing postoperative muscle strength with the median nerve as the recipient nerve was 13, and the pooled sample size was 281. Three publications, out of all of the publications, were excluded from the meta-analysis because they had a muscle strength recovery efficiency rate of either 100% or 0%. Owing to the relatively poor homogeneity among these studies ($P = 0.002$, $I^2 = 66.2\%$), a random-effects model was employed here. The WMD was 0.50, and the 95% CI was 0.39–0.61. The overall muscle strength recovery efficiency rate after CC7 nerve transfer was 0.50. The detailed results are shown in Figure 4a.

The results of the bias detection analysis are shown in Figure 4b. The results suggest that there might be a publication bias.

Sensory recovery efficiency rate

The total number of studies assessing postoperative sensory recovery with the median nerve used as the recipient nerve

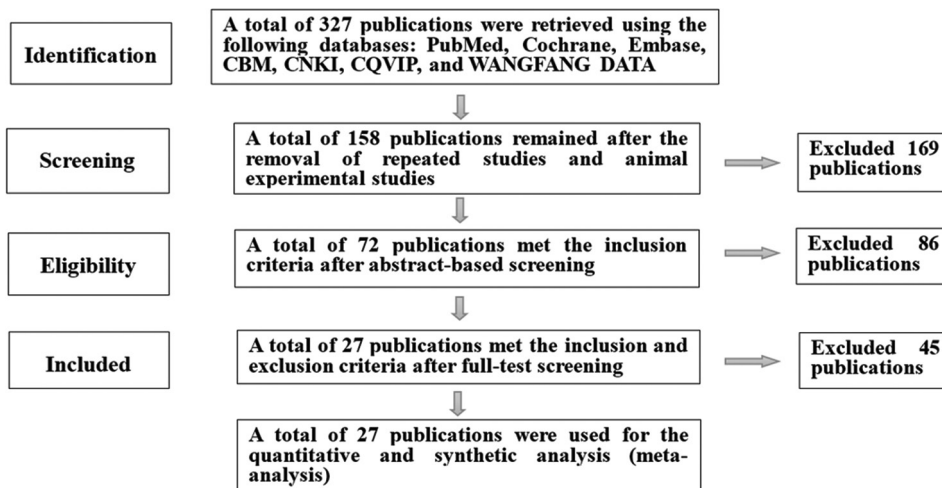


Figure 1: A Preferred Reporting Items for Meta-Analyses protocol flowchart illustrating the selection of studies included in our systematic review.

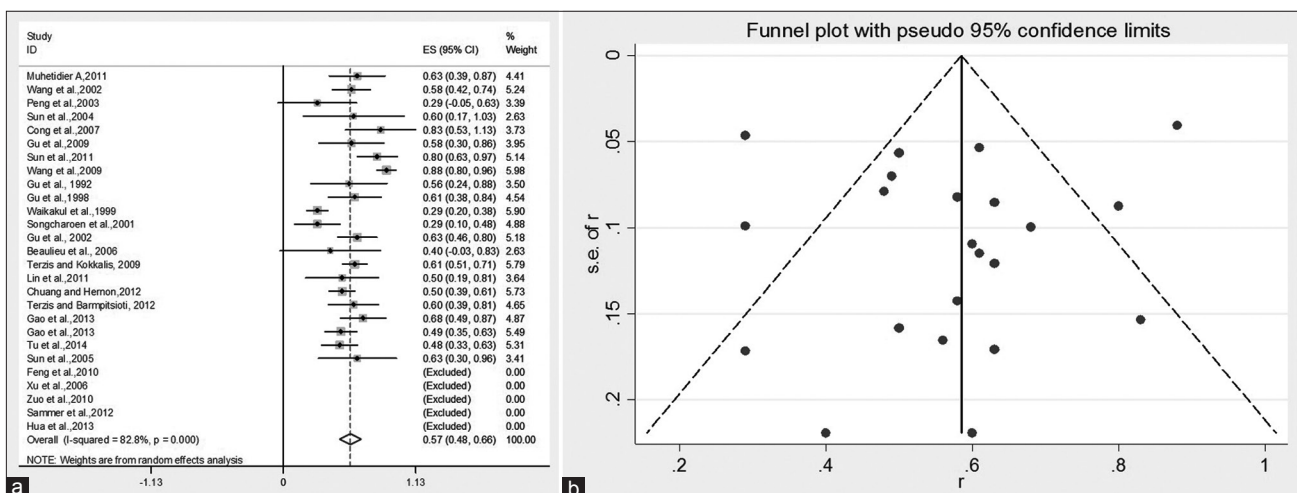


Figure 2: Meta-analysis of the muscle strength recovery efficiency rate for all recipient nerves (a) and its funnel plot (b).

Table 1: Chinese literature data extraction

Study	Location	Number of patients	Average age (years)	Type of injury	Time between injury and surgery (months)	Follow-up average time or time ranges (months)	Recipient nerve	Recovery rate (%)
Muhetidir, 2011 ^[2]	Xinjiang Medical University, China	16	30.5	Total BPAI	1–12	6–25	Median nerve, radial nerve, and musculocutaneous nerve	63
Wang <i>et al.</i> , 2002 ^[3]	Shanghai Huashan Hospital, China	36	27	Total BPAI	9.4 (3–36)	38 (24–84)	Radial nerve	58
Peng <i>et al.</i> , 2003 ^[4]	Shanghai Huashan Hospital, China	7	24.4	Total BPAI (2 cases) and partial brachial plexus root avulsion	NA	6–15	6 upper trunk; 1 lower trunk	29
Sun <i>et al.</i> , 2004 ^[5]	Shanghai Huashan Hospital, China	5	21.5	Total BPAI	NA	12–19	Ulnar nerve; sural nerve	60
Feng, 2010 ^[6]	Shanghai Huashan Hospital, China	4	26	Total BPAI	2 (0.8–5)	26–38	2 lower trunk; 2 C8-T1	100
Cong <i>et al.</i> , 2007 ^[7]	Wendeng Orthopedic Hospital of Shandong Province, China	6	33	Total BPAI	2 (0.3–6)	13–18	Upper trunk	83
Gu <i>et al.</i> , 2009 ^[8]	The First Affiliated Hospital of Sun Yat-Sen University, China	12	23	Total BPAI	2 (1–3)	9–36	Upper trunk; lower trunk; C6 nerve root; C8 nerve root	58
Sun, 2011 ^[9]	The Third Hospital of Hebei Medical University, China	21	27.7	Traumatic brachial plexus C5-T1 avulsion	4.8 (1–18)	35.7 (1–76)	Upper trunk; radial nerve; median nerve	80
Wang <i>et al.</i> , 2010 ^[10]	Beijing Jishuitan Hospital, China	64	26	Total BPAI (60 cases); middle and lower trunk avulsion (4 cases)	3.7 (1–18)	44 (36–57)	56 lower trunk; 8 medial cord	88
Sun <i>et al.</i> , 2005 ^[11]	Shanghai, China	8	28	Total BPAI	6	21	Median nerve, radial nerve, and musculocutaneous nerve	63

BPAI: Brachial plexus avulsion injury; NA: Not available.

was 11, and the pooled sample size was 211. One study that reported a recovery rate of 100% was excluded from the meta-analysis. Owing to the relative homogeneity among these studies ($I^2 = 11.3\%$), a fixed-effects model was employed here. The WMD was 0.56, and the 95% *CI* was 0.50–0.63. The overall sensory recovery efficiency rate after CC7 operation was 0.56. The detailed results are shown in Figure 5a.

The bias detection results are shown in Figure 5b. The results suggest that there might be a publication bias.

Musculocutaneous nerve as recipient nerve Muscle strength recovery efficiency rate

The total number of studies reporting the grading of postoperative muscle strength with the musculocutaneous nerve used as the recipient nerve was nine, and the pooled sample size was 95. Owing to the homogeneity among these studies ($I^2 = 0\%$), a fixed-effects model was employed here. The WMD was 0.74, and the 95% *CI* was 0.65–0.82. The overall muscle strength recovery efficiency rate after CC7 operation was 0.74. The detailed results are shown in Figure 6a.

Table 2: English literature data extraction

Study	Location	Number of patients	Average age (years)	Injury type	Preoperative period (months)	Follow-up average time or time range (months)	Recipient nerve	Recovery rate (%)	Motor recovery Wrist and finger flexion and extension		
									M4	M3	<M3
Gu <i>et al.</i> , 1992 ^[12]	Shanghai, China	9	37	Total BPAI	11	31	Median nerve, radial nerve, and musculocutaneous nerve	56	5	0	4
Gu <i>et al.</i> , 1998 ^[13]	Shanghai, China	18	26	Total BPAI	12	41	Median nerve, radial nerve, and musculocutaneous nerve	61	7	4	7
Waikakul <i>et al.</i> , 1999 ^[14]	Bangkok, Thailand	96	27	Total BPAI	3	36	Median nerve	29	0	28	68
Songcharoen <i>et al.</i> , 2001 ^[15]	Bangkok, Thailand	21	25	Total BPAI	5	42	Median nerve	29	0	6	15
Gu <i>et al.</i> , 2002 ^[16]	Shanghai, China	32	26	Total BPAI	10	24	Musculocutaneous nerve and radial nerve	63	20	12	
Xu <i>et al.</i> , 2006 ^[17]	Shanghai, China	2	27	Total BPAI	7	29	Median nerve	100	0	2	0
Beaulieu <i>et al.</i> , 2006 ^[18]	Paris, France	5	32	Total BPAI	4	20	Musculocutaneous nerve	40	2	0	3
Terzis and Kokkalis, 2009 ^[19]	Norfolk, VA, USA	83	23	NA	30	73	Median nerve, radial nerve, musculocutaneous nerve, and triceps brachii nerve	61	31	20	32
Zuo <i>et al.</i> , 2010 ^[20]	Shanghai, China	8	25	Total BPAI	5	68	Median nerve	100	4	4	0
Lin <i>et al.</i> , 2011 ^[21]	Shanghai, China	10	26	Total BPAI	4	39	Median nerve	50	0	5	5
Chuang and Hemon, 2012 ^[22]	Taoyuan, China Taipei, China	78	26	NA	4	48	Median nerve	50	0	39	39
Terzis and Barmptsioti, 2012 ^[23]	Norfolk, VA, USA	20	26	NA	17	56	Triceps brachii nerve	60	5	7	8
Sammer <i>et al.</i> , 2012 ^[24]	Rochester, NY, USA	15	27	NA	5	40	Median nerve	0	0	0	15
Gao <i>et al.</i> , 2013 ^[25]	Shanghai, China	22	26	Total BPAI	5	76	Median nerve	68	0	15	7
Gao <i>et al.</i> , 2013 ^[26]	Shanghai, China	51	29	Total BPAI	NA	83	Median nerve	49	0	25	26
Hua <i>et al.</i> , 2013 ^[27]	Shanghai, China	5	25	Total BPAI	2	71	Median nerve	100	3	2	0
Tu <i>et al.</i> , 2014 ^[28]	Tainan, China Taipei, China	40	27	Total BPAI	4	72	Median nerve	48	5	14	21

BPAI: Brachial plexus avulsion injury; NA: Not available.

The bias detection results are as shown in Figure 6b. The results suggest that there might be a publication bias.

Radial nerve as recipient nerve Muscle strength recovery efficiency rate

The total number of studies assessing postoperative muscle strength when the radial nerve was used as the recipient nerve was nine, and the pooled sample size was 24. Owing

to the homogeneity among these studies ($I^2 = 0\%$), a fixed-effects model was employed here. The WMD was 0.50, and the 95% CI was 0.31–0.70. The overall muscle strength recovery efficiency rate after CC7 operation was 0.50. The detailed results are shown in Figure 7a.

The bias detection results are shown in Figure 7b. The figure is relatively symmetrical. However, the sample

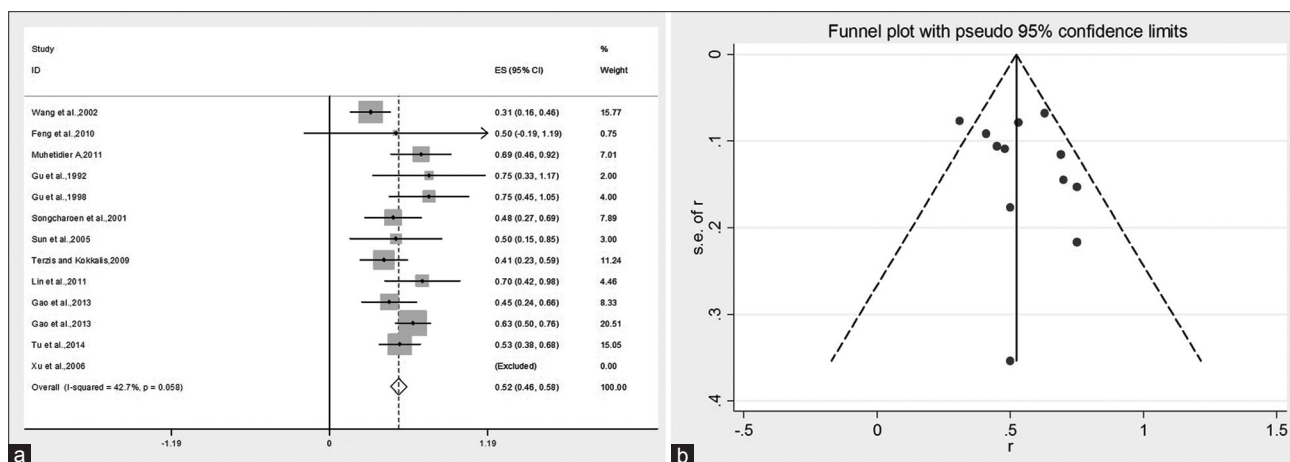


Figure 3: Meta-analysis of the sensory recovery efficiency rate of all recipient nerves (a) and its funnel plot (b).

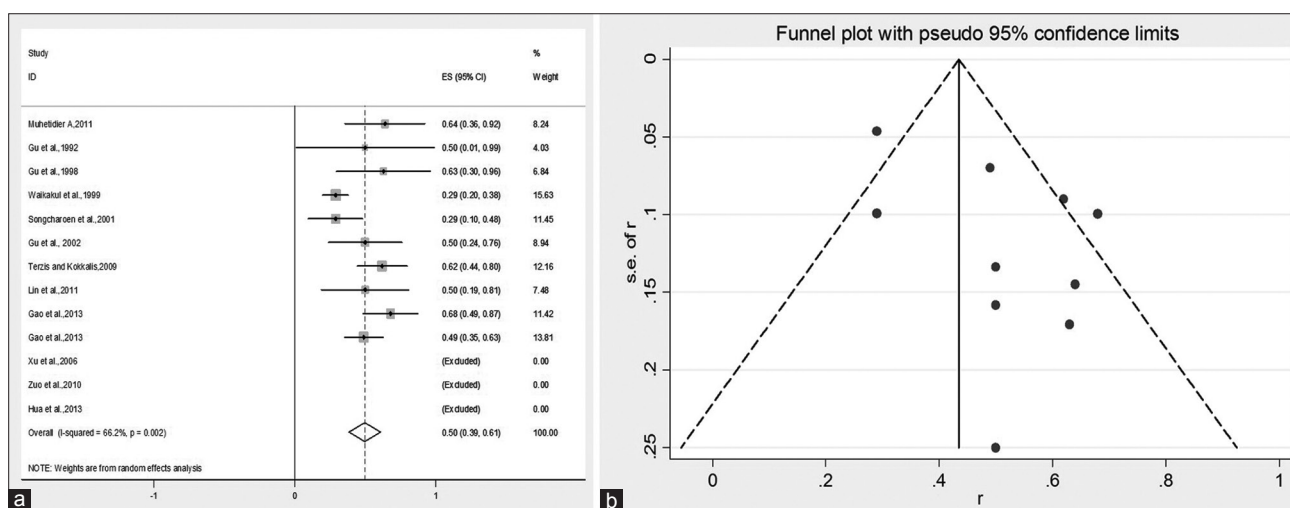


Figure 4: Meta-analysis of the muscle strength recovery efficiency rate when the median nerve was used as the recipient nerve (a) and its funnel plot (b).

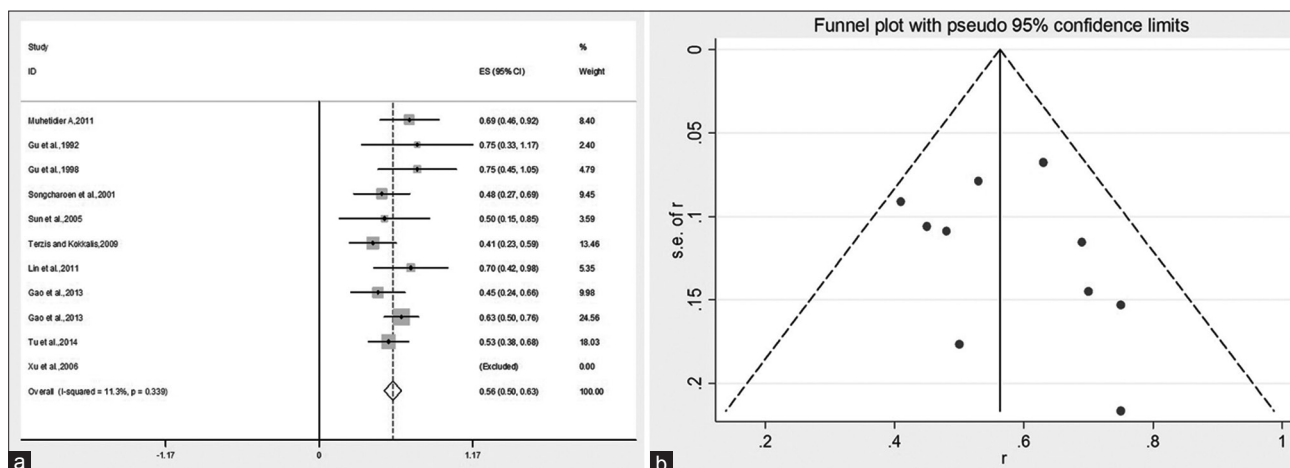


Figure 5: Meta-analysis of the sensory recovery rate for the median nerve when it was used as the recipient nerve (a) and its funnel plot (b).

size is quite small. The inspection of the plot showed low efficiency.

DISCUSSION

By combining the results of multiple similar studies, a

meta-analysis can increase statistical power and thus leads to a more robust estimation of a measure. Meta-analysis results are widely accepted by clinicians as high-quality evidence to support their clinical practices. In this study, although most of the available data were extracted from these

original articles with limited sample sizes, we included all evidence that we concerned in medical practice to evaluate the overall outcomes for yielding strong recommendations. We conducted a full-text search using Chinese keywords or English keywords (“contralateral c-7,” “contralateral c7,” “c7 nerve root,” and “seventh cervical nerve root”) with databases at home and aboard. Our aims were to (1) comprehensively retrieve publications about the effect of CC7 nerve transfer on ipsilateral sensory and muscle strength, (2) conduct a meta-analysis of the data extracted from reported clinical cases, and (3) draw scientifically valid conclusions about the effects of CC7 nerve transfer on ipsilateral sensory and muscle strength.

Muscle strength recovery is considered to be effective only when a score of M3 or higher in the MRC rating system is achieved, while sensory recovery is considered to be effective only when the achieved score is S3 or higher. The results of the complete meta-analysis are shown in Table 3. Where no distinction was made between recipient nerves, the meta-analysis showed that the muscle strength

recovery efficiency rate after CC7 nerve transfer was 0.57 (95% CI: 0.48–0.66), and the sensory recovery efficiency rate was 0.52 (95% CI: 0.46–0.58). When the recipient nerve was the median nerve, the muscle strength recovery rate after CC7 nerve transfer was 0.50 (95% CI: 0.39–0.61), and the sensory recovery rate was 0.56 (95% CI: 0.50–0.63). When the recipient nerve was the musculocutaneous nerve, the muscle strength recovery rate after CC7 nerve transfer was 0.74 (95% CI: 0.65–0.82). When the recipient nerve was the radial nerve, the muscle strength recovery efficiency rate after CC7 nerve transfer was 0.50 (95% CI: 0.31–0.70).

This meta-analysis shows that, with regard to muscle strength, transfer of the CC7 nerve to the musculocutaneous nerve leads to the best outcome, while transfer of the CC7 nerve to the median or radial nerve leads to outcomes that are similar to each other but inferior to a transfer to the musculocutaneous nerve. These results suggest that when modifying surgical approaches, surgeons should consider using the musculocutaneous nerve as a recipient nerve for repairing brachial plexus injury [Table 3].

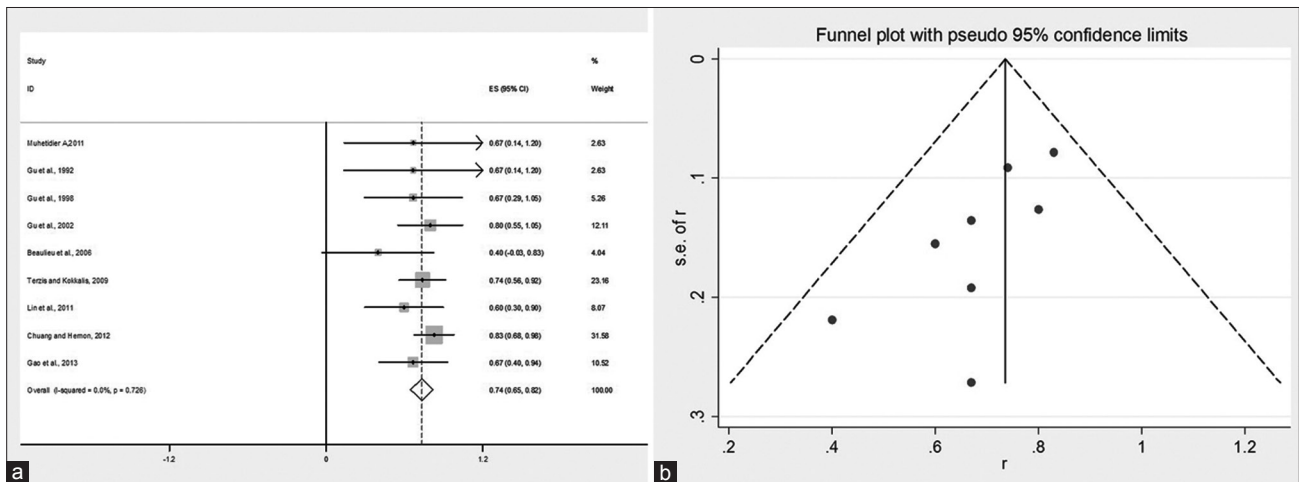


Figure 6: Meta-analysis of muscle strength recovery efficiency rate when the musculocutaneous nerve was used as the recipient nerve (a) and its funnel plot (b).

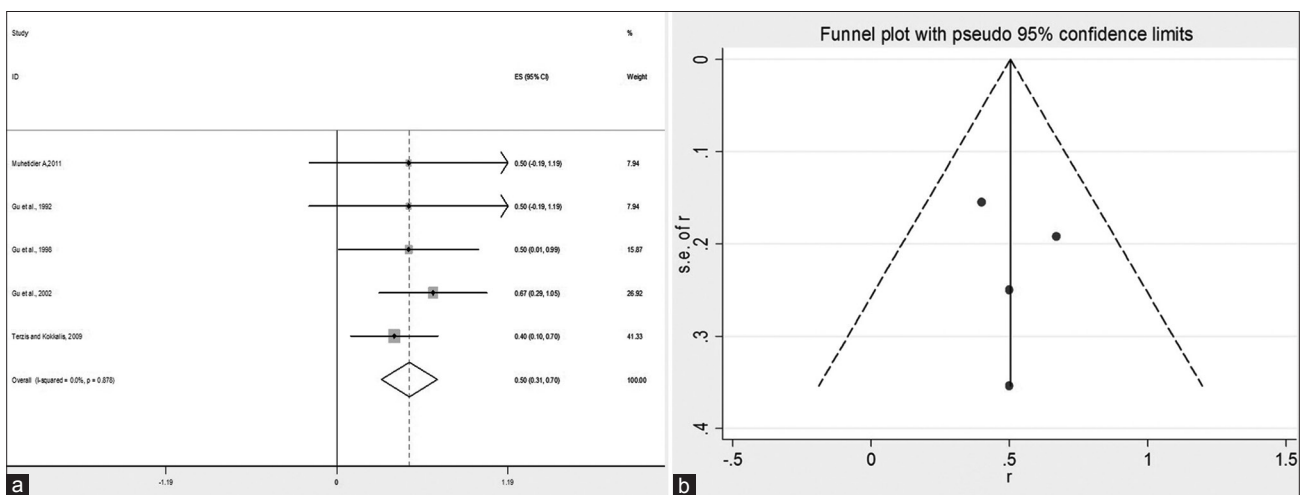


Figure 7: Meta-analysis of muscle strength recovery efficiency rate when the radial nerve was used as the recipient nerve (a) and its funnel plot (b).

Table 3: Results of the meta-analysis on recovery rates of muscle strength and sensory recovery for different recipient nerves

Recipient nerve	Muscle strength recovery rate	95% CI	Sensory recovery rate	95% CI
Pooled	0.57	0.48–0.66	0.52	0.46–0.58
Median nerve	0.50	0.39–0.61	0.56	0.50–0.63
Musculocutaneous nerve	0.74	0.65–0.82	–	–
Radial nerve	0.50	0.31–0.70	–	–

–: Not applicable; CI: Confidence interval.

We observed that most of the muscle strength and sensory recovery efficiency rates were in the range of 50–60%, which was slightly lower than those reported in other studies; the difference between our data range and those reported elsewhere could be attributed to the fact that we rigorously recruited patients with scores \geq M3/S3, while other studies allowed for wider score ranges when recruiting patients and included patients with scores of M2/S2.^[1]

After CC7 nerve transfer, the patient is encouraged to perform more exercises of the healthy limb, especially elbow extension and shoulder adduction, thus to stimulate regeneration from CC7 toward the injured side along the nerve graft. In the early stage of functional recovery, all patients experience problem with involuntary movement of the injured arm the motion has to be initiated by the movement of the healthy arm which is meaning co-contraction movement. Therefore, of paramount importance after CC7 transfer is successful transformation of cortical plasticity, which is the bottom line for voluntary motion of the patient, and we therefore investigated the final sample regarding this factor. Since our sample only contained four publications^[2,17,19,26] which mentioned brain reorganization, we were not able to perform a meta-analysis on such a small sample. However, the promising consensus among these publications is that cortical remodeling may continue for a long period after peripheral rearrangement, possibly more than 5 years, and that motor control of the reinnervated limb may eventually reorganize from the ipsilateral to the contralateral hemisphere exclusively, instead of activating the bilateral neural network. The quicker limb function recovers, the more active patients are, the stronger muscle strength is, the faster the cerebral cortex will be remodeled.

The analyses presented here have several limitations, outlined in the following. (1) Although the total number of articles included in the meta-analysis was large, different recipient nerves were only distinguished in a limited number of publications; in this subsample, only data from the median nerves, radial nerves, and musculocutaneous nerves were reported, while data from other types of nerves such as the triceps brachii nerves were not reported. We could therefore not include other nerves into our comparison. (2) In the included publications, the samples in the preoperative periods

were significantly different from those in the follow-up period, regarding a variety of potentially confounding factors that were difficult to exclude; we could therefore not conduct a stratified analysis. These factors may affect the results of this meta-analysis. (3) The age of the participants was not made clear in all studies. Although one of the inclusion criteria adopted was a mean age above 18 years, some studies recruited a number of participants who were younger, while the mean age of all recruited participants remained above 18 years, thereby giving rise to potential biases. (4) The included articles did not provide any distinction between the muscle strength of wrist flexion and finger flexion. (5) Different surgical approaches were employed. Traditional surgical procedures are usually divided into two stages. In the first stage, the ulnar nerve is cut at the ipsilateral wrist region, passed through the axilla and chest via the subcutaneous passage, and anastomosed to the CC7 nerve root at the contralateral cervical region. In the second stage, the ulnar nerve is anastomosed to the recipient nerve, usually 1 year after the first stage. Cong *et al.*^[7] and Wang *et al.*^[10] conducted nerve transfer via the pre-spinal route and achieved good outcomes. However, this surgical approach is rather complex and is likely to result in complications.^[29,30] Meanwhile, some surgeons have explored a third-stage surgical procedure after the second-stage surgery. (6) The patients' self-exercise might affect the recovery efficiency rate.

We did not do the safety analysis because we could not find suitable data in the included publications in this study; however, according to our previous study,^[29] the complication of CC7 transfer through modified pre-spinal route was 2.6% which related to C7 transection. Among them, only 0.24% patients need reoperation for function reconstruction.

In conclusion, based on our quantitative analysis, CC7 is a reliable donor nerve, can be safely used for upper limb function reconstruction, especially for total BPAIs. We recommend that the recipient nerve can be radial nerve, median nerve, and musculocutaneous nerve. However, on comparison, the latter is the best. For modifying procedure, we recommend that the median nerve and musculocutaneous nerve can be recipient nerve together for CC7 transfer to repair BPAI.

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Conflicts of interest

There are no conflicts of interest.

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