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Research progress in rehabilitation treatment of stroke patients

A bibliometric analysis[☆]

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Abstract

BACKGROUND: Stroke presents as a transient or chronic brain dysfunction and is associated with high morbidity and high mortality. The doctors and scientists would like to argue how to enhance the validity of the rehabilitation treatment and how to further improve the level of treatment on stroke.

OBJECTIVE: The aim of this study was to quantitatively analyze the current worldwide progress in research on stroke rehabilitation treatment based on Web of Science database and ClinicalTrials.gov in the past 10 years.

METHODS: We conducted a quantitative analysis of clinical trial articles regarding stroke rehabilitation published in English from 2003 to 2013 and indexed in the National Institutes of Health Clinical Trials registry and Web of Science databases. Data were downloaded on March 15, 2013.

RESULTS: (1) From 2003 to 2013, 2 654 clinical trials investigating stroke were indexed in ClinicalTrials.gov. There were only 58 clinical trials registered in 2003, and there was a marked increase from 2005. A total of 605 clinical trials on the rehabilitation of stroke were conducted in the past 10 years. (2) The analysis showed that most of the trials in the field were registered by North American institutions. With respect to the Asian countries, China and Taiwan area of China also published a reasonable proportion of the trials, but comparatively speaking, the number of trials is really rare. Most of the interventions were drugs, followed by the devices, and behavioral interventions were ranked third. (3) In the past 10 years, there were 4 052 studies on stroke indexed by Web of Science database.

CONCLUSION: From perspective of research progress, we found that the number of clinical trials and papers on stroke rehabilitation has increased significantly in the past 10 years, between them a remarkable positive correlation exists.

Key Words

neural regeneration; reviews; stroke; rehabilitation; treatment; Web of Science; National Institutes of Health; Clinical Trials registry database; bibliometric analysis; neuroregeneration

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INTRODUCTION

Stroke is one of the most common refractory diseases, and has serious consequences for human health and safety. It is estimated that there are nearly 2 million stroke patients in China each year. The incidence of stroke is as high as 201/100 000; there are 7 million surviving stroke patients, 4.5 million of whom have varying degrees of work incapacity or cannot take care of themselves and with high disability rate.

Patients would like to recover as soon as possible after stroke. Scientists also would like to see their discoveries help people with stroke. Physicians, surgeons and therapists want the treatments they provide to improve an individual's independence, mobility and quality of life.

Clinical trials is a very important way to improve the level of treatment, it can determine if a promising stroke rehabilitation treatment is safe and effective for patients, and can be approved by the regulatory authorities. With respect to the treatment and rehabilitation on stroke patients, these trials may evaluate drugs already approved for other diseases to assess if the drug may be useful for stroke rehabilitation. They may also evaluate new experimental drugs to determine if they improve motor function, recovery of linguistic function, slow disease progression or even prevent stroke for patients following stroke.

In this paper, a quantitative analysis was conducted to investigate programs registered in the National Institutes of Health (NIH) Clinical Trials registry (ClinicalTrial.gov) for quantitative analysis of stroke rehabilitation treatment research. We also collected data from the Web of Science database on research funding bodies and trials on stroke rehabilitation to provide an understanding of international research trends in stroke rehabilitation treatment over the past 10 years.

MATERIALS AND METHODS

Data retrieval

(1) The search was primarily undertaken on the online version of the Clinical Trials registry database from 2003. ClinicalTrial.gov recorded 30 102 trials up to March, 2013. (2) Web of Science was searched to identify articles published on various clinical treatments on stroke rehabilitation, especially using deep brain stimulation, aspirin, stem cell transplantation and Chinese medicine.

Inclusion criteria

- (1) Articles on the clinical treatment of stroke with stem cell transplantation or physiotherapy (e.g. exercise, electro-stimulation) and other rehabilitation methods.
- (2) Types of articles including original research, proceedings paper, notes, letters, editorial material, discussion and book chapters.
- (3) Year of publication: 2003–2013.
- (4) Citation databases: Science Citation Index Expanded.
- (5) Quantitative analysis of clinical trials on stroke rehabilitation treatment recorded in ClinicalTrial.gov from 2003 to present.

Exclusion criteria

- (1) Processing clinical trials.
- (2) Ahead of publication articles.

Key words

Key words used for stroke rehabilitation treatment included: (1) “stroke” and “rehabilitation”; (2) “stroke” and “treatment”; (3) “stroke” and “deep brain stimulation”; (4) “stroke” and “aspirin”; (5) “stroke” and “stem cell transplantation”; (6) “stroke” and “Chinese medicine”.

Data analysis

The statistical analysis of ClinicalTrial.gov and Web of Science data was performed in MS Excel. The outcomes of all trials and articles referring to treatment on stroke rehabilitation were selected and analyzed using the following measurements: (1) overall number of trials; (2) distribution of output by region on trials; (3) distribution of output in countries on trials; (4) distribution of output in institutions on trials; (5) number of publications annually; (6) number of citations received annually; (7) top cited papers.

RESULTS

ClinicalTrial.gov

Together with the US Food and Drug Administration, the National Library of Medicine of the NIH established ClinicalTrials.gov in 2000–2002. ClinicalTrials.gov aims to report timely clinical trial information of the US Pharmaceutical Industry Association and other national government agencies. It also focuses on providing patients, their families, medical and health workers and the public with related information. NIH requires the clinical trials to include experimental therapy on serious or life-threatening diseases, and the clinical trials should cover all countries and privately funded trials. Its purpose is to disseminate clinical trial reports worldwide *via* the Internet.

With respect to the clinical trials on stroke between 2003 and 2013, there were 2 654 clinical trials in total, and the age group is divided into eight subunits, and most of the recruitments are adults (97%). Concerning the status, 474 trials were Phase 2 or Phase 2 | Phase 3.

Distribution of output by country

ClinicalTrials.gov currently lists 144 845 studies with locations in all 50 American states and in 185 countries. ClinicalTrials.gov receives more than 95 million page views per month and 60 000 unique visitors daily (as of February 2012). With respect to all 102 817 of the registered trials, the United States was ranked first with 59 492 clinical trials (41%), whereas China had much less activity with only 7 420 clinical trials. The regional distribution of clinical trials on stroke rehabilitation is listed in Table 1.

Region Names	Number of studies
World	605
Africa	3
Central America	2
East Asia	70
Europe	130
Middle East	25
North America	324
North Asia	10
Pacifica	15
South America	4
South Asia	6
Southeast Asia	16

Of the 605 clinical trials on stroke rehabilitation, the United States had the highest number with 252 studies, followed by Canada with 72 studies. Europe also performed well with 130 studies. Comparatively speaking, East Asia did well on stroke rehabilitation, accounting for 70 trials, with the highest number in Taiwan area of China with 39 studies, followed by China mainland with 16, of which the clinical trials on Chinese medicine and acupuncture treatment performed well, and accounted for 43% of the total Chinese completed trials. Republic of Korea with nine, Hong Kong Special Administrative Region of China with five and Japan with three.

Distribution of output of sponsors/collaborators

With respect to the funding institutions, the US Department of Veterans Affairs (VA) sponsored the highest number of studies, 46 trials. The VA is a government-run military veteran benefit system with Cabinet-level status, and the second largest US government department, after the Department of Defense^[5] (Table 2).

Funding institution	Number of studies
Department of Veterans Affairs	46
Eunice Kennedy Shriver National Institute of Child Health and Human Development	21
Chang Gung Memorial Hospital	10
Emory University	8
Assistance Publique-Hôpitaux de Paris	7
Capital District Health Authority, Canada	6
Allergan	5
American Heart Association	5
AMES Technology	5
Burke Rehabilitation Hospital	5

The Eunice Kennedy Shriver National Institute of Child Health and Human Development tended to be trial-intensive. With 21 studies, it ranked second among the top 10 institutions, followed by Chang Gung Memorial Hospital, Taiwan area of China, with 10 studies.

Clinical trials in China

There were 16 Chinese trials on stroke rehabilitation in ClinicalTrials.gov, seven were finished (Table 3), one was in enrolling by invitation, the recruiting status remains 5, but also include three unknown trials.

Title	Condition	Interventions	Registry No.
Efficiency study of traditional Chinese medicine (TCM) versus western medicine (WM) on ischemic stroke	Stroke	Acupuncture, massage and basic TCM treatment; rehabilitation and WM basic treatment	NCT008 43765
Can acupuncture benefit surgical patients with hemorrhagic stroke?	Stroke	Acupuncture; conventional rehabilitation	NCT010 37894
Transcranial alternating current stimulation	Stroke	Transcranial alternating current stimulation	NCT012 00719
Effect of speed-dependent treadmill training in patients with subacute stroke	Stroke	Transcranial alternating current stimulation	NCT013 28301
A spinal functional magnetic resonance imaging (fMRI) study of resting-state, motor task and acupoint stimulation	Cerebral infarction	Motor task, sensory stimulation	NCT006 29655
To document the effectiveness of bont-a injection in adult subjects with upper limb spasticity following stroke	Muscle spasticity		NCT010 20500
Establishment and evaluation of the effects of a clinical pathway for acute ischemic stroke	Acute ischemic stroke	Drug: aspirin, Chinese herbs	NCT009 66316

Annual publication outputs on stroke rehabilitation in Web of Science between 2003 and 2013

Evidence-based medicine has emerged as a valuable tool to guide clinical decision-making by providing evidence for both diagnostic and treatment strategies^[2]. There were 9 674 articles on stroke rehabilitation cited in Web of Science from 2003 to 2013. The number of publications on stroke rehabilitation grew steadily from 521 in 2003 to 1 416 in 2012, a 2.7-fold increase (Figure 1). This illustrates the dynamism in this area of medical research and indicates that greater priority has been given to investigation of stroke rehabilitation therapies.

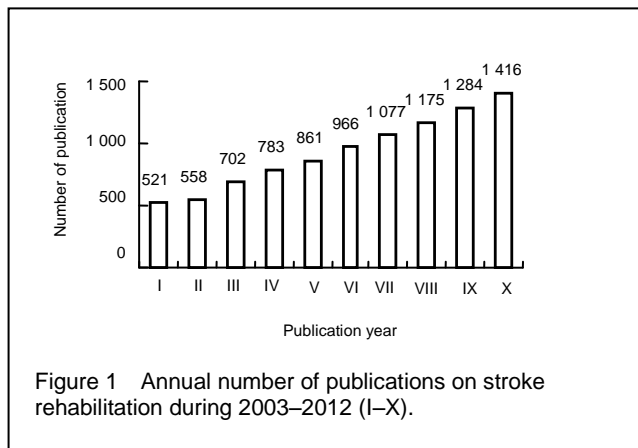


Figure 1 Annual number of publications on stroke rehabilitation during 2003–2012 (I–X).

Top 10 institutions for publication output in Web of Science during 2003–2013

From 2003 to 2013, the top 10 universities or institutions that published the most papers on stroke rehabilitation came from the United States, Canada or the United Kingdom (Table 4).

Institution	Number of studies	% of total records
State University System of Florida	205	2.1
University of Toronto	200	2.0
University of London	197	2.0
Northwestern University	184	1.9
University of California	183	1.8
University of Florida	178	1.8
Harvard University	150	1.5
University of Western Ontario	146	1.5
Rehabilitation Institute of Chicago	138	1.4
McGill University	136	1.4

The State University System of Florida, the University of Toronto and the University of London were the three institutions with the highest output in terms of total number of stroke rehabilitation studies published, with 205, 200 and 197, respectively.

Top 10 cited papers on stroke rehabilitation (Table 5)

Title	Publication year	Total citations	Average per year
Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke-The EXCITE randomized clinical trial ^[3]	2006	530	88.33
Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke ^[4]	2005	313	44.71
Exercise plus behavioral management in patients with Alzheimer disease-A randomized controlled trial ^[5]	2003	254	28.22
Insulin therapy protects the central and peripheral nervous system of intensive care patients ^[6]	2005	239	34.14
Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe-Data from a multicenter multinational hospital-based registry ^[7]	2003	199	22.11
Weight-supported treadmill vs overground training for walking after acute incomplete SCI ^[8]	2006	195	32.50
Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open-protocol study ^[9]	2005	191	27.28
Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the american heart association/american stroke association ^[10]	2010	187	93.50
Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke ^[11]	2005	186	26.57
Effects of robotic therapy on motor impairment and recovery in chronic stroke ^[12]	2003	185	20.55

The 10 publications on stroke rehabilitation in Web of Science from 2003 to 2013 with the highest number of citations are presented in Table 6. Research on stroke rehabilitation was mainly published in the following journals indexed on Web of Science: *Archives of Physical Medicine and Rehabilitation, Stroke, Disability and Rehabilitation, Neurorehabilitation and Neural Repair, Clinical Rehabilitation*. The top cited paper does not necessarily equate to the highest impact paper on an annual basis.

Top cited papers on stroke rehabilitation treatment using deep brain stimulation

Deep brain stimulation is a minimally invasive targeted neurosurgical intervention that enables structures deep

in the brain to be stimulated electrically by an implanted pacemaker^[13]. The most cited research on deep brain stimulation in stroke rehabilitation concerns methods and protocols (Table 6).

Table 6 Top cited papers on stroke rehabilitation treatment using deep brain stimulation

Title	Publication year	Total citation	Average citation per year
Transcallosal inhibition in chronic subcortical stroke ^[14]	2005	96	13.71
Overt naming fMRI pre- and post-TMS: Two nonfluent aphasia patients, with and without improved naming post-TMS ^[15]	2009	44	14.66
Updates on the use of non-invasive brain stimulation in physical and rehabilitation medicine ^[16]	2009	32	10.66
Results by motor cortex stimulation in treatment of focal dystonia, Parkinson's disease and post-ictal spasticity. The experience of the Italian Study Group of the Italian Neurosurgical Society ^[17]	2008	10	2.5
Effects of somatosensory stimulation on the excitability of the unaffected hemisphere in chronic stroke patients ^[18]	2008	2	0.66

Top cited papers on stroke rehabilitation treatment using aspirin

Studies have shown that aspirin used for secondary prevention significantly reduces cardiovascular and stroke risk. The data for aspirin and primary prevention of cardiovascular disease, and in particular stroke, are less clear, especially among black people^[19] (Table 7).

Top cited papers on stroke rehabilitation treatment using stem cell transplantation

The treatment of ischemic stroke remains a daunting task as few therapeutic strategies have proven to be effective. Recent research on the use of stem cells holds great promise for the treatment of many diseases, including stroke (Table 8). Bone marrow-derived stem cells have gained particular attention, because of that they are easily obtained, and can differentiate into different lineages under specific conditions without ethical questions^[25].

Top cited papers on stroke rehabilitation treatment using Chinese medicine and acupuncture

Most acupuncture studies on stroke rehabilitation are published in alternative and complementary medicine

journals, which focus on studies of traditional Chinese medicine. Only 13 articles on acupuncture treatment could be retrieved, of which 80% were published by Chinese researchers and clinicians. The five most cited papers in Web of Science on the use of Chinese medicine and acupuncture in stroke rehabilitation are displayed in Table 9.

Table 7 Top cited papers on stroke rehabilitation treatment using aspirin

Title	Publication year	Total citation	Average citation per year
Can we improve the statistical analysis of stroke trials? Statistical reanalysis of functional outcomes in stroke trials ^[20]	2007	49	9.8
A "poly-portfolio" for secondary prevention: A strategy to reduce subsequent events by up to 97% over five years ^[21]	2005	31	4.42
Prevention of deep venous thrombosis and pulmonary embolism following stroke: a systematic review of published articles ^[22]	2007	19	3.8
Management of lower extremity peripheral arterial disease ^[23]	2008	15	3.75
Oral carriage of yeasts and coliforms in stroke sufferers: a prospective longitudinal study ^[24]	2008	10	2.5

Table 8 Top cited papers on stroke rehabilitation treatment using stem cell transplantation

Title	Publication date	Total citation	Average citation per year
Recovery and rehabilitation in stroke - Stem cells ^[26]	2004	54	6.75
Transplantation of human embryonic stem cell-derived neural precursor cells and enriched environment after cortical stroke in rats: cell survival and functional recovery ^[27]	2009	39	13.00
Stem Cell Therapies as an Emerging Paradigm in Stroke (STEPS) Bridging Basic and Clinical Science for Cellular and Neurogenic Factor Therapy in Treating Stroke ^[28]	2009	34	11.33
Transplantation of hNT neurons into the ischemic cortex: cell survival and effect on sensorimotor behavior ^[29]	2006	34	5.66
Mesenchymal stem cells transplantation could be beneficial for treatment of experimental ischemic stroke in rats ^[30]	2008	24	6.00

Table 9 Top cited papers on stroke rehabilitation treatment using Chinese medicine and acupuncture

Title	Publication year	Total citation	Average citation per year
Acupuncture for upper-extremity rehabilitation in chronic stroke: a randomized sham-controlled study ^[31]	2005	28	4.00
Acupuncture for acute stroke-art. no. CD003317.pub2 ^[32]	2005	24	3.42
Acupuncture for stroke rehabilitation ^[33]	2006	16	2.66
Effects of Meridian acupressure for stroke patients in Korea ^[34]	2009	8	2.66
Chinese medicine pattern differentiation and its implications for clinical practice ^[35]	2011	7	7.00

DISCUSSION

In the bibliometric analysis and systematic review, there were 2 654 clinical trials regarding stroke in ClinicalTrials.gov from 2003 to 2013, of which 605 trials addressed stroke rehabilitation.

Analysis of the distribution of countries in which the trials were performed revealed that North America and some European countries were most likely to conduct clinical trials before therapies or medicines were introduced into practice. The comparatively small number of trials in most Asian countries, including China, may indicate that the importance of clinical trials has not been fully recognized. Because of language differences, resources, regulatory procedural timelines, and the general understanding of clinical research, China is only now taking steps in this regard, but there are many problems to be studied and many measures to be taken, so there is a long way ahead.

Because of the limited selection of journals on acupuncture and traditional Chinese medicine included in Web of Science, the number of publications in Web of Science on the use of Chinese medicine and acupuncture in stroke rehabilitation was much less than the number of publications on other rehabilitation studies. Stroke is the leading cause of disability and the second most common cause of death in the Western world^[36]. Currently, no clinical treatment can be found that restores neurological function after stroke. Stem cell transplantation holds great promise for facilitating recovery after stroke and has thus become a popular topic for researchers and scientists.

It can be surprisingly difficult to find out if a treatment or therapy is safe and if it really works. If a patient receives an experimental therapy and experiences some recovery, he/she generally believes this was a direct result of the new treatment. However, the improvement may not have been caused by the treatment. Thus, for people who have received an experimental drug or cell transplant, it can be difficult to tell whether recovery was a result of unrecognized spontaneous healing, the effects of rehabilitation, or the effect of the experimental treatment. Effective clinical trials are designed to accurately and reliably determine which of these possibilities the cause of any observed recovery is. Clinical trials can benefit scientists, clinicians and patients. If an experimental therapy has not accomplished a properly designed clinical trial program, there is a real danger that treatment does not work or therapies that might do harm could become standard medical care.

There is widespread consensus that rehabilitation exercises maximize the possibility of greater independence for activities of daily living and improve mobility. Physical and occupational rehabilitation training is now widely available. Comparatively speaking, most of the completed Chinese clinical trials on stroke rehabilitation are about Chinese medicine and acupuncture, which means that the Chinese medicine and acupuncture have been accepted and trusted by the worldwide scientists and researchers in some degree. However, what we must admit is that our performance on ClinicalTrials.gov is still weak, we should begin to give priority to the clinical trials like the United States and other European countries.

As long as we realize the importance and significance of clinical trials, we will provide the drug discovery and experimental therapies much safer and more effective recovery, which in turn will make more and more patients and families benefit from this meaningful conduction. In fact, not only the patients would benefit from the registration, but also it would offer the countries more opportunities to face the whole world and to keep in pace with the advances in scientific fields.

Finally, the journals focusing on physical medicine were found to have the most articles on rehabilitation studies after stroke.

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manuscript. Xiaodong Feng critically revised the manuscript. All authors approved the final version of the paper.

Conflicts of interest: None declared.

Ethical approval: The experiment was conducted according to the institutional guidelines with the protocol approved by the Ethics Committee of Henan University of Traditional Chinese Medicine.

Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application disputations.

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