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Use of nerve conduits for peripheral nerve injury repair

A Web of Science-based literature analysis★

Jinniang Nan, Xuguang Hu, Hongxiu Li, Xiaonong Zhang, Renjing Piao

Department of General Surgery, Second People's Hospital of Panjin, Panjin 124000, Liaoning Province, China

Abstract
OBJECTIVE: To identify global research trends in the use of nerve conduits for peripheral nerve injury repair.
DATA RETRIEVAL: Numerous basic and clinical studies on nerve conduits for peripheral nerve injury repair were performed between 2002–2011. We performed a bibliometric analysis of the institutions, authors, and hot topics in the field, from the Web of Science, using the key words peripheral nerve and conduit or tube.
SELECTION CRITERIA: Inclusion criteria: peer-reviewed published articles on nerve conduits for peripheral nerve injury repair, indexed in the Web of Science; original research articles, reviews, meeting abstracts, proceedings papers, book chapters, editorial material, and news items. Exclusion criteria: articles requiring manual searching or telephone access; documents not published in the public domain; and several corrected papers.
MAIN OUTCOME MEASURES: (a) Annual publication output; (b) publication type; (c) publication by research field; (d) publication by journal; (e) publication by funding agency; (f) publication by author; (g) publication by country and institution; (h) publications by institution in China; (i) most-cited papers.
RESULTS: A total of 793 publications on the use of nerve conduits for peripheral nerve injury repair were retrieved from the Web of Science between 2002–2011. The number of publications gradually increased over the 10-year study period. Articles constituted the main type of publication. The most prolific journals were *Biomaterials*, *Microsurgery, and Journal of Biomedical Materials Research Part A*. The National Natural Science Foundation of China supported 27 papers, more than any other funding agency. Of the 793 publications, almost half came from American and Chinese authors and institutions.
CONCLUSION: Nerve conduits have been studied extensively for peripheral nerve regeneration; however, many problems remain in this field, which are difficult for researchers to reach a consensus.

Key Words
nerve conduit; biomaterial; axon; neurotrophic factor; stem cell; extracellular matrix; peripheral nerve injury; peripheral nerve repair; degradation; biocompatibility; neural regeneration

Research Highlights
(1) We performed a bibliometric analysis of studies published during 2002–2011 retrieved from the Web of Science on the use of nerve conduits for peripheral nerve injury repair.
(2) We analyzed the publication year, type, research field, journal, funding agency, author, country, and institution.
(3) We analyzed the institutions and authors depending on the number of publications. We especially analyzed the publication patterns of Chinese institutions and authors to provide information on the research status of this field in China.

Jinniang Nan★, Master, Department of General Surgery, Second People's Hospital of Panjin, Panjin 124000, Liaoning Province, China

Corresponding author: Hongxiu Li, M.D., Chief physician, Master's supervisor, Department of General Surgery, Second People's Hospital of Panjin, Panjin 124000, Liaoning Province, China

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INTRODUCTION

Peripheral nerve injury is a common clinical disease, and its incidence is much higher than central nervous system injury. Under suitable conditions, axons on the proximal side of the damaged peripheral nerve can regenerate the original nerve functions through sprouting regeneration[1-2]. Prior to this, the severed ends must re-aggregate so that the axonal growth cone can grow smoothly in right direction towards the endoneurial tube on the distal side, before it can reinnervate the target organs and re-dominate the intrinsical domain[3-5]. In the case of nerve tissue defects, direct anastomosis of the severed nerve can cause tension, which can result in hyperplasia of fibrous tissue near the anastomotic stoma, thereby seriously obstructing axonal growth. Thus, physicians mainly choose nerve autografting in the case of large defects to avoid anastomotic tension on the nerve and ensure successful axonal regeneration[4-8]. However, this method has some unavoidable disadvantages: additional surgeries are required to obtain a donor nerve; functional lesions occur at the donor site; there are limited sources of donor nerve; autografting cannot repair wide or severe neurological defects, especially in cases of brachial plexus injury[9-11]. For these reasons, researchers have been continually exploring the use of neural conduits to bridge nerve defects, so that one day they will be able to effectively replace autologous transplantation. The discovery and application of nerve conduits has had some success. Furthermore, as nerve conduits are fabricated from biological or synthetic materials, they do not require any donor tissue from other parts of the nervous system.

In this study, we analyzed the research trends in the use of nerve conduits for the repair of peripheral nerve injury, based on a bibliometric analysis of papers from the Web of Science during 2002–2011.

DATA SOURCES AND METHODOLOGY

Data retrieval

This study used bibliometric analyses to quantitatively and qualitatively investigate research trends in studies of nerve conduits for peripheral nerve injury repair. We searched the Web of Science, a research database of publications and citations selected and evaluated by the Institute for Scientific Information in Philadelphia, PA, USA, using the key words peripheral nerve and conduit or tube. We limited the period of publication from 2002–2011, and compiled a bibliography of all articles related to nerve conduits for peripheral nerve injury repair. All data were downloaded on August 12, 2012.

Inclusion criteria

The inclusion criteria were as follows: (1) published peer-reviewed articles on the use of nerve conduits for peripheral nerve injury repair, including original research articles, reviews, meeting abstracts, proceedings papers, book chapters, editorial material, and news items, which were indexed in the Web of Science; (2) published between 2002-2011; and (3) the citation database was the Science Citation Index Expanded.

Exclusion criteria

We excluded articles that required manual searching or telephone access, documents that were not published in the public domain, and several corrected papers from the total articles analyzed.

The outcomes of all articles referring to the use of nerve conduits for peripheral nerve injury repair were assessed using the following criteria: (a) annual publication output; (b) type of publication; (c) publication by research field; (d) publication by journal; (e) publication by funding agency; (f) publication by author; (g) publication by country and institution; (h) publication by institution in China; (i) most-cited papers.

RESULTS

Output by year of publications relating to nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011 (Figure 1)

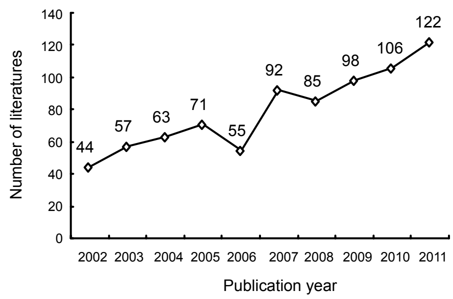

Figure 1 Output by year of publications on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011.

A total of 793 publications on nerve conduits for peripheral nerve injury repair were retrieved from Web of Science, 2002–2011. The number of relevant publications gradually increased over the 10-year study period, with 44 papers published and included in the Web of Science in 2002, increasing to 122 in 2011. Numbers of papers published slightly decreased in 2006 and 2008.

Different types of publications relating to nerve conduits for peripheral nerve injury repair during 2002–2011

Articles constituted the major type of publication relating to nerve conduits for the repair of peripheral nerve injury during this period (Figure 2), with 617 articles. The other types were proceedings papers, reviews, meeting abstracts, letters, book chapters, corrections, and editorial material.

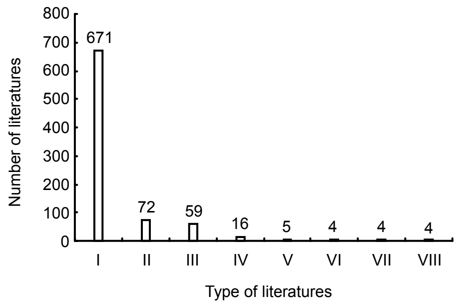

Figure 2 Types of publications on nerve conduits for peripheral nerve injury repair included in the Web of Science during 2002–2011.

I: Articles; II: proceedings papers; III: reviews; IV: meeting abstracts; V: letters; VI: book chapters; VII: corrections; VIII: editorial materials.

Distribution by research field of publications on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011

Among the research fields represented in publications relating to the use of nerve conduits for the repair of peripheral nerve injury in the Web of Science during 2002–2011, 221 papers were in the field of neuroscience/neurology. The second best-represented field, with 218 papers, was engineering. In the fields of materials science and surgery, 188 papers were published on the use of nerve conduits for the repair of peripheral nerve injury (Table 1).

Table 1 Distribution by research field of publications on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011

Research field	No. of papers	% of total publications
Neurosciences neurology	221	27.869
Engineering	218	27.491
Materials science	188	23.707
Surgery	188	23.707
Biotechnology applied microbiology	78	9.836
Cell biology	75	9.458
Orthopedics	30	3.783
Biochemistry molecular biology	29	3.657
Polymer science	27	3.405
General internal medicine	25	3.153

Output by journal of publications on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011

In the period of interest, *Biomaterials* published 50 papers, followed by *Microsurgery* and *Journal of Biomedical Materials Research Part A*, which published 41 and 35 papers, respectively. The other eight top journals were *Tissue Engineering Part A*, *Journal of Reconstructive Microsurgery*, *Experimental Neurology*, *Annals of Plastic Surgery*, *Journal of Materials Science Materials in Medicine*, *Journal of Neuroscience Methods*, *Neural Regeneration Research*, and *Neurological Research* (Table 2).

Distribution by funding agency for publications on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011

Among the publications, 27 articles were supported by the National Natural Science Foundation of China, and 18 articles each were supported by the National Institutes of Health, and the National Science Council of the Republic of China, Taiwan. Most of the funding agencies were in China (Table 3).

Table 2 Top 11 journals for publications on nerve conduits for peripheral nerve injury repair from 2002 to 2011

Journal	ISSN	Journal country	Impact factor	No. of papers	% of total publications
Biomaterials	0142-9612	Netherlands	7.404	50	6.305
Microsurgery	0738-1085	USA	1.605	41	5.170
Journal of Biomedical Materials Research Part A	1549-3296	USA	2.625	35	4.414
Tissue Engineering Part A	1937-3341	USA	–	20	2.522
Journal of Reconstructive Microsurgery	0743-684X	USA	1.432	19	2.396
Experimental Neurology	0014-4886	USA	4.699	15	1.892
Annals of Plastic Surgery	0148-7043	USA	1.318	14	1.765
Journal of Materials Science Materials in Medicine	0957-4530	Netherlands	2.316	14	1.765
Journal of Neuroscience Methods	0165-0270	Netherlands	1.980	14	1.765
Neural Regeneration Research	1673-5374	China	0.216	13	1.639
Neurological Research	0161-6412	USA	1.522	13	1.639

Table 3 The top 10 funding agencies on nerve conduits for peripheral nerve injury repair from 2002 to 2011

Funding agency	No. of papers	% of total publications
National Natural Science Foundation of China	27	3.405
National Institutes of Health	18	2.270
National Science Council of the Republic of China Taiwan	18	2.270
High-Tech R&D Program of China (863 Program)	8	1.008
National Science Foundation	6	0.757
Chinese National Natural Science Youth Fund	5	0.631
National Basic Research Program of China	5	0.631
Taiwan Department of Health Clinical Trial and Research Center of Excellence	5	0.631
China Medical University	4	0.504
Chinese 973 Project Planning	4	0.504

Distribution by author for publications on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011

Giorgio Terenghi published 27 papers (3.405%) on nerve conduits for the repair of peripheral nerve injury, which is much more than any other author (Table 4). Mikael Wiberg ranked second with 19 papers (2.396%), Stefano Geuna and Shan-Hui Hsu ranked third with 18 papers (2.27%).

Table 4 Top 12 authors publishing papers on nerve conduits for peripheral nerve injury repair included in the Web of Science during 2002–2011

Author	No. of papers	% of total publications
Giorgio Terenghi	27	3.405
Mikael Wiberg	19	2.396
Stefano Geuna	18	2.270
Shan-Hui Hsu	18	2.270
Yueh-Sheng Chen	17	2.144
Chun-Hsu Yao	17	2.144
Susan E. Mackinnon	16	2.018
Xavier Navarro	15	1.892
Paul J. Kingham	14	1.765
Hisham Fansa	13	1.639
Xiaosong Gu	13	1.639
Gerburg Keilhoff	13	1.639

Output by country and institution of publications on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011

Analysis of the contributions of different countries/states to publications was based on journal articles in which the address and affiliation of at least one author were provided. A total of 793 articles were analyzed by country and institution. Most papers on nerve conduits for the repair of peripheral nerve injury were published in USA (206 papers), which was followed second by China (177 papers) (Figure 3). The University of Manchester, Umeå University, Kyoto University and Washington University were the most prolific research institutes (Table 5).

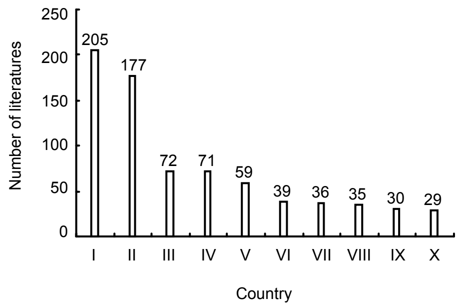

Figure 3 The top 12 countries publishing papers on nerve conduits for peripheral nerve injury repair during 2002–2011.

I: USA; II: China; III: Germany; IV: Japan; V: UK; VI: Italy; VII: Sweden; VIII: Canada; IX: Switzerland; X: Netherlands.

Table 5 The top 10 institutes publishing papers on nerve conduits for peripheral nerve injury repair during 2002–2011

Institute	No. of papers	% of total publications
University of Manchester	25	3.153
Umeå University	24	3.026
Kyoto University	22	2.774
Washington University	22	2.774
National Chung Hsing University	20	2.522
University of Turin	18	2.270
Tsinghua University	18	2.270
China Medical University	16	2.018
Universitat Autonoma de Barcelona	16	2.018
University of California system	15	1.892

Distribution by institutes in China for publications on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011

Tsinghua University was the most prolific research institute in China for the publication of papers on nerve conduits for repair of peripheral nerve injury in the Web of Science during 2002–2011 (Table 6). Nantong University, Donghua University, Peking University, and Shanghai Jiao Tong University published more than 10 papers in this field.

Highly cited papers on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011

Of the 793 papers on nerve conduits for the repair of peripheral nerve injury cited in the Web of Science during 2002–2011, the 2007 paper, "Guidance of glial cell migration and axonal growth on electrospun nanofibers of poly-epsilon-caprolactone and a collagen/poly-epsilon-caprolactone blend"[12], published in *Biomaterials*, was the most cited paper, with 189 citations. Of the 10 most-cited papers, four were published in *Biomaterials*, and the remaining six were published in six different journals; four were published in 2002, and two each were published in the years 2003, 2005, 2007 and 2008 (Table 7).

Table 6 The top 12 Chinese institutes publishing papers on nerve conduits for peripheral nerve injury repair during 2002–2011

Institute	No. of papers	% of total publications
Tsinghua University	18	14.4
Nantong University	14	11.2
Donghua University	13	10.4
Peking University	11	8.8
Shanghai Jiao Tong University	11	8.8
Sun Yat-sen University	7	5.6
Fudan University	5	4.0
Wuhan Univ Technol	5	4.0
Fourth Military Medical University	3	2.4
Shandong University	3	2.4
Third Military Medical University	3	2.4
Wuhan University	3	2.4

Highly cited papers on nerve conduits for peripheral nerve injury repair published by Chinese authors or institutions in the Web of Science during 2002–2011

A total of 177 papers on nerve conduits for the repair of peripheral nerve injury published by Chinese authors or institutions were indexed in the Web of Science during 2002–2011 (Table 8). The 2004 paper, "Evaluation of biocompatibility of polypyrrole *in vitro* and *in vivo*"[26], published by *Journal of Biomedical Materials Research Part A* was cited 98 times—more times than any other paper in this group. Of the 10 most-cited papers, three were published in *Biomaterials*, and the remaining seven were published in seven different journals; four were published in 2007, and two each were published in the years 2004, 2005, 2006, and 2008.

DISCUSSION

Our bibliometric analysis, based on the Web of Science, identified several research trends in studies of nerve conduits for the repair of peripheral nerve injury over the past decade. The number of publications gradually increased over the 10-year study period, and most were articles. The most prolific journals in this area were *Biomaterials*, *Microsurgery*, and *Journal of Biomedical Materials Research Part A*. Of the 793 publications retrieved from the Web of Science during 2002–2011, almost half came from American and Chinese authors and institutions.

To date, a great quantity of literature has been published on the application of nerve conduits for the repair of small nerve defects, with some success.

Table 7 The 10 top-cited papers on nerve conduits for peripheral nerve injury repair in the Web of Science during 2002–2011

Title	Author	Journal	Publication year	Total citations	Average per year
Guidance of glial cell. migration and axonal growth on electrospun nanofibers of poly-epsilon-caprolactone and a collagen/poly-epsilon-caprolactone blend [12]	Schnell E, Klinkhammer K, Balzer S, *et al*.	*Biomaterials*	2007	189	31.50
Pre-existing pathways promote precise projection patterns[13]	Nguyen QT, Sanes JR, Lichtman JW.	*Nature Neuroscience*	2002	132	12.00
Controlled release of nerve growth factor enhances sciatic nerve regeneration[14]	Lee AC, Yu VM, Lowe JB 3rd, *et al*.	*Experimental Neurology*	2003	131	13.10
Bioactive poly(L-lactic acid) conduits seeded with Schwann cells for peripheral nerve regeneration[15]	Evans GR, Brandt K, Katz S, *et al*.	*Biomaterials*	2002	127	11.55
Directional guidance of oligodendroglial migration by class 3 semaphorins and netrin-1[16]	Spassky N, de Castro F, Le Bras B, *et al*.	*Journal of Neuroscience*	2002	115	10.45
Biocompatibility analysis of poly(glycerol sebacate) as a nerve guide material[17]	Sundback CA, Shyu JY, Wang Y, *et al*.	*Biomaterials*	2005	111	13.88
Enhancement of neurite outgrowth using nano-structured scaffolds coupled with laminin[18]	Koh HS, Yong T, Chan CK, *et al.*	*Biomaterials*	2008	109	21.80
Aligned protein-polymer composite fibers enhance nerve regeneration: a potential tissue-engineering platform[19]	Chew SY, Mi R, Hoke A, *et al.*	*Advanced Functional Materials*	2007	106	17.67
Clinical use of nerve conduits in peripheral-nerve repair: review of the literature[20]	Meek MF, Coert JH	*Journal of Reconstructive Microsurgery*	2002	106	9.64
Nerve repair by means of tubulization: literature review and personal clinical experience comparing biological and synthetic conduits for sensory nerve repair[21]	Battiston B, Geuna S, Ferrero M, *et al.*	*Microsurgery*	2005	103	12.88

Table 8 The 10 top-cited papers on nerve conduits for peripheral nerve injury repair from Chinese authors or institutions during 2002–2011

Title	Author	Journal	Publication year	Total citations	Average per year
Evaluation of biocompatibility of polypyrrole *in vitro* and *in vivo* [22]	Wang X, Gu X, Yuan C, *et al.*	*Journal of Biomedical Materials Research Part A*	2004	98	10.89
The interaction of Schwann cells with chitosan membranes and fibers *in vitro*[23]	Yuan Y, Zhang P, Yang Y, *et al*.	*Biomaterials*	2004	83	9.22
Biocompatibility evaluation of silk fibroin with peripheral nerve tissues and cells *in vitro*[24]	Yang Y, Chen X, Ding F, *et al.*	*Biomaterials*	2007	77	12.83
Dog sciatic nerve regeneration across a 30-mm defect bridged by a chitosan/PGA artificial nerve graft[25]	Wang X, Hu W, Cao Y, *et al*.	*Brain*	2005	74	9.25
Development and evaluation of silk fibroin-based nerve grafts used for peripheral nerve regeneration[26]	Yang Y, Ding F, Wu J, *et al*.	*Biomaterials*	2007	68	13.60
Repair of extended peripheral nerve lesions in rhesus monkeys using acellular allogenic nerve grafts implanted with autologous mesenchymal stem cells[27]	Hu J, Zhu QT, Liu XL, *et al*.	*Experimental Neurology*	2007	40	6.67
Nerve conduit filled with GDNF gene-modified Schwann cells enhances regeneration of the peripheral nerve[28]	Li Q, Ping P, Jiang H, *et al*.	*Microsurgery*	2006	39	5.57
Tissue-engineered peripheral nerve grafting by differentiated bone marrow stromal cells[29]	Hou SY, Zhang HY, Quan DP, *et al.*	*Neuroscience*	2006	37	5.29
Degradation of covalently cross-linked carboxymethyl chitosan and its potential application for peripheral nerve regeneration[30]	Lu GY, Kong LJ, Sheng BY, *et al*.	*European Polymer Journal*	2007	33	5.50
Electrospun nanofibers immobilized with collagen for neural stem cells culture[31]	Li W, Guo Y, Wang H, *et al*.	*Journal of Materials Science-Materials in Medicine*	2008	32	6.40

However, the application of nerve conduits for the repair of long segmental nerve defects has had poor results[32-35]. Although there were a large number of studies on nerve conduit materials, no single material has been shown to be superior to autografts in performance[36]. The reason for this could be the lack of an ideal structure and biological constituents to repair peripheral nerve defects, or the lack of extracellular matrix and Schwann cells, all of which are important factors for the repair of peripheral nerve defects. Numerous studies have suggested that the design concept of the nerve conduits is very important[37-42]. The following are a list of properties that are believed to be important for developing an optimal conduit: biocompatibility, good flexibility, mechanical support, appropriate degradation velocity, neutral degradation products from polymer conduits, thickness, porosity, pore size, and wall micro-structure. Ideally the morphological characteristics of the conduit should be similar to the extracellular matrix. Nerve conduits alone are difficult for the repair of long segmental nerve defects. Neurotrophic factors and stem cells can be introduced into the conduit lumen to form a composite nerve conduit. These conduits not only serve to bridge the nerve gap, but also create a good microenvironment for nerve regeneration, with neurotrophic factors inducing chemotactic effects[43-51]. We look forward to the day when a nerve conduit is created that meets the physiological and biological requirements for promoting effective nerve repair.

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Conflicts of interest: None declared.

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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