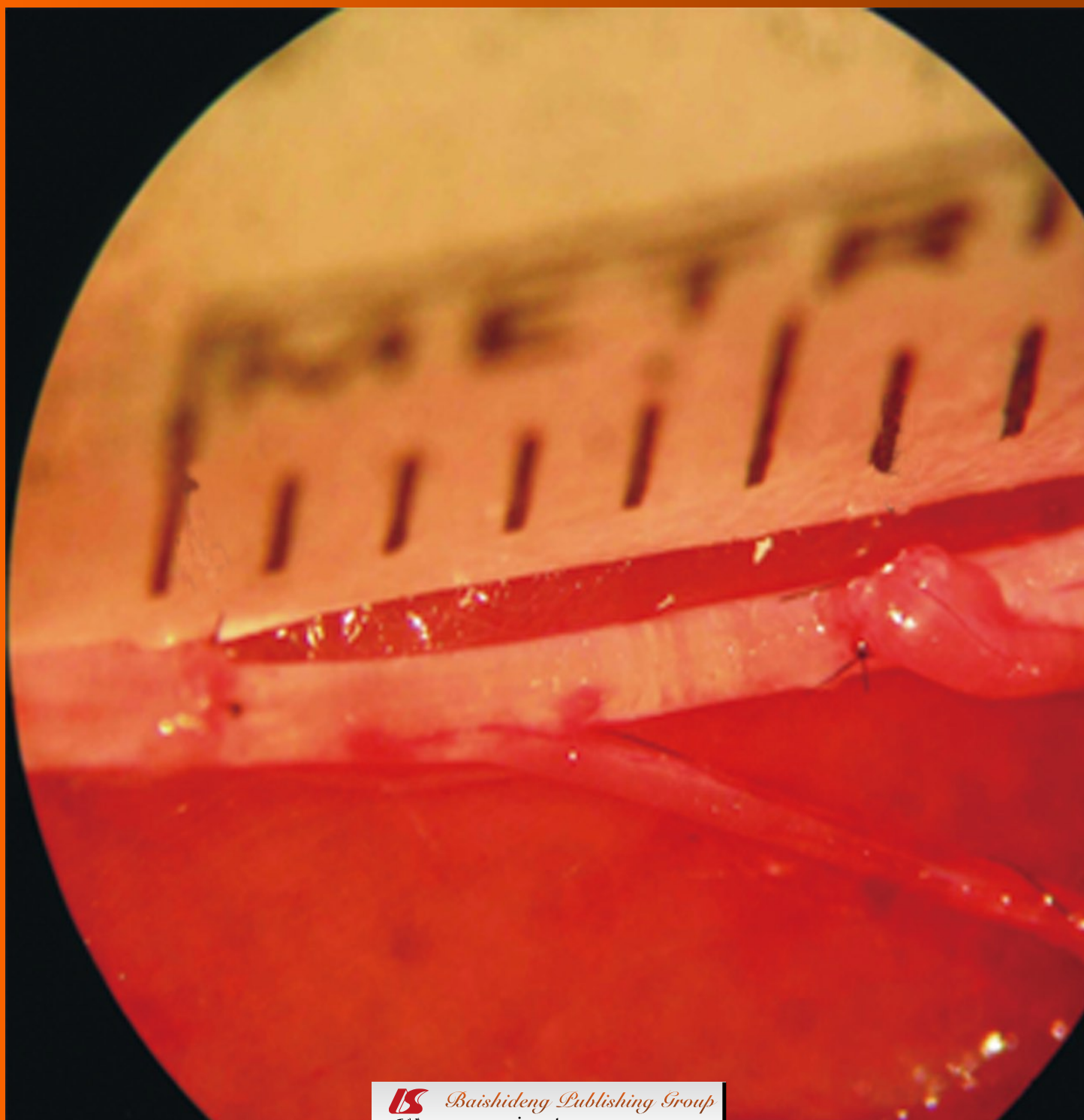


World Journal of *Orthopedics*

World J Orthop 2011 November 18; 2(11): 102-106





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EDITORIAL

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Lykissas MG

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World J Orthop 2011; 2(11): 102-106
<http://www.wjgnet.com/2218-5836/full/v2/i11/102.htm>

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World Journal of Orthopedics (*World J Orthop*, *WJO*, online ISSN 2218-5836, DOI: 10.5312) is a monthly peer-reviewed, online, open-access, journal supported by an editorial board consisting of 245 experts in orthopedics from 30 countries.

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World Journal of Orthopedics

LAUNCH DATE
November 18, 2010

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PUBLICATION DATE
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ISSN
ISSN 2218-5836 (online)

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Current concepts in end-to-side neurorrhaphy

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Received: May 18, 2011 Revised: October 2, 2011

Accepted: October 9, 2011

Published online: November 18, 2011

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Lykissas MG. Current concepts in end-to-side neurorrhaphy. *World J Orthop* 2011; 2(11): 102-106 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v2/i11/102.htm> DOI: <http://dx.doi.org/10.5312/wjo.v2.i11.102>

Abstract

In peripheral nerve injury, end-to-side neurorrhaphy involves coaptation of the distal stump of a transected nerve to the trunk of an adjacent donor nerve. It has been proposed as an alternative technique when the proximal stump of an injured nerve is unavailable or the nerve gap is too long to be bridged by a nerve graft. Experimental and clinical data suggests that end-to-side neurorrhaphy can provide satisfactory functional recovery for the recipient nerve, without any deterioration of the donor nerve function. The most accepted mechanism of nerve regeneration following end-to-side neurorrhaphy is collateral sprouting. The source of the regenerating axons traveling in the epineurium of the donor nerve is thought to be the proximal Ranvier's nodes at the site of end-to-side neurorrhaphy, however, histologic evidence is still lacking. Partial neurotomy of the donor nerve may enhance regeneration of motor neurons through end-to-side neurorrhaphy and reinnervation of motor targets.

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Key words: End-to-side neurorrhaphy; Collateral sprouting; Nerve regeneration; Peripheral nerve injury

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INTRODUCTION

Autologous nerve grafting remains the gold standard for the management of nerve gaps following peripheral nerve injury. Use of autologous nerve grafts is bounded by the limited amount of available tissue and the increased donor site morbidity. Several surgical alternatives have been reported with various success. These include the combination of nerve grafts and silicon tubes^[1], the use of synthetic or biologic nerve conduits^[2], tubes containing blood vessels^[3], the application of cultured Schwann cells^[4] and end-to-side neurorrhaphy.

It was not until 1992, when Viterbo *et al*^[5] reintroduced end-to-side neurorrhaphy, an almost forgotten technique of nerve coaptation. End-to-side neurorrhaphy involves coaptation of the distal stump of a transected nerve to the trunk of an adjacent donor nerve. It has been proposed as an alternative technique in cases of peripheral nerve injury, when the proximal stump of an injured nerve is unavailable or obliterated or the nerve gap is too long to be bridged by a nerve graft^[6-8].

End-to-side neurorrhaphy was first described by Lettievant in 1873 as a reconstructive strategy of peripheral nerves in cases of large substance loss^[9]. The pioneer

s idea was abandoned due to poor results that can be attributed to the use of conventional surgical instruments and non-microsurgical techniques without the use of a microscope. Almost nine decades later, many investigators have again experimented using this interesting technique^[5,10-15]. The results this time were very promising and since then, many studies have been performed resulting in improvement of functional results and further understanding of nerve regeneration after end-to-side neurorrhaphy.

COLLATERAL SPROUTING

The most accepted mechanism of nerve regeneration following end-to-side neurorrhaphy is collateral sprouting, where regenerated axons emerge from the most proximal Ranvier's node of the donor nerve to the coaptation site and travel in the epineurium of the donor nerve^[16-25]. Before axonal development, schwann cells are organized into columns at the coaptation site^[26]. At a later stage, these cells invade the epineurial layer of the recipient nerve. This is considered the critical step for the initiation of collateral axonal sprouting from the intact axons. It is supported that axons emerge from the Ranvier's nodes of the donor nerve proximal to the coaptation site^[25,27-29]. According to one study, Schwann cells were found to stimulate axonal regeneration from both the distal nerve stump and Ranvier's nodes of the donor nerve^[30].

The mechanism causing collateral sprouting after end-to-side neurorrhaphy may result from switching signals and/or switching factors, presumably neurotrophic^[19]. Zhang *et al*^[19] suggested that factors released from the Schwann cells, which have migrated to the epineurium, are transferred into the perineurium by diffusion and promote collateral sprouting from the closest to the injury site to Ranvier's nodes of the donor nerve.

It is well known that Neurotrophine-3 (NT-3) plays a distinct role in the processes of nerve regeneration and muscle reinnervation^[25]. NT-3 and its receptor Trk C are expressed in the coaptation site following end-to-side neurorrhaphy^[31]. Growth-associated protein-43 (GAP-43), a marker of growth cone formation, brain-derived neurotrophic factor (BDNF) and Trk B (BDNF receptor) are also detected in the coaptation site in lower concentrations and after NT-3 expression^[31]. In an end-to-side neurorrhaphy model using anti-GAP-43 antibody, growth cone direction was recorded from the donor nerve to the peripheral nerve segment of the injured nerve.

Many investigators have also shown the distinct role of nerve growth factor (NGF) during collateral sprouting^[32-37]. NGF is produced in end-organs following nerve injury. The secreted NGF is taken up by the axon terminals and transported retrogradely to the nerve cell body stimulating a secondary response. It has been shown that the combination of NGF and ciliary neurotrophic factor (CNTF) promotes axonal regeneration after end-to-side neurorrhaphy^[38].

FACTORS AFFECTING MOTOR REGENERATION

Biological responses of the donor neuron to factors emanating from the transected nerve have been implicated in the initiation of collateral sprouting for both sensory and motor axons. According to previous studies, significant motor functional recovery after end-to-side neurorrhaphy can be achieved without donor nerve axotomy^[39,40]. However, more recent studies suggest that donor nerve injury, such as axotomy or suturing, is required for motor reinnervation of the recipient nerve^[41,42].

Bontioti *et al*^[41] revealed increased expression of activating transcription factor 3 (ATF3), a marker of cell activation induced in sensory and motor neurons following peripheral nerve injury, after the creation of an epineurial window and/or suturing. According to these findings, an operative injury to the donor nerve during end-to-side neurorrhaphy is the main prerequisite for axonal sprouting.

A dose-response relationship between axotomy of the donor nerve and motor axons regeneration has been demonstrated^[42]. Presumably, motor fibers from the donor nerve may enter the recipient nerve segment to supply muscles which were normally innervated by motor fibers from the recipient nerve^[43].

DOUBLE END-TO-SIDE NEURORRHAPHY

Viterbo *et al*^[13] first described double end-to-side neurorrhaphy. In this technique, both proximal and distal stumps of the recipient nerve are coapted in an end-to-side fashion to the trunk of an adjacent donor nerve (Figure 1). The regenerated axons use the epineurium of the donor nerve as a bridge to find the distal stump. It has been suggested that this technique stimulates axonal growth by a supercharged effect compared with end-to-end repair. Interestingly, when double end-to-side neurorrhaphy was compared with the conventional end-to-side technique, the recipient nerve following the double terminolateral technique was found to contain a significantly larger number of myelinated nerve fibers distal to the neurorrhaphy site^[44]. Two sources of axons may contribute to the increased number of regenerating nerve fibers, axons sprouted collaterally from myelinated nerve fibers at the node of Ranvier of the donor nerve, and axons that arise from the proximally coapted nerve segment.

Our experimental knowledge of double end-to-side neurorrhaphy, leads us to the belief that double end-to-side coaptation may be a valuable tool when the classic end-to-end technique is not possible. In our previous studies in rats, functional evaluation and axonal counting data demonstrated that nerve regeneration can be supported using the intact nerve bridge technique for a distance of 1.2 cm in a rat sciatic model^[44].

Epineurial vs perineurial window

A technical parameter that may significantly affect axonal

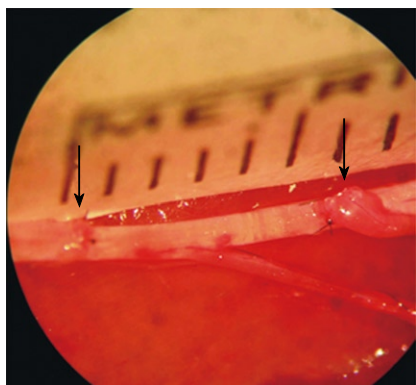


Figure 1 Double end-to-side neurorrhaphy with 0.6-cm regeneration distance between the proximal and distal stump of the recipient nerve (black arrows). In both neurorrhaphies, coaptation was performed with 3 interrupted 9-0 nylon sutures placed at 120°.

regeneration after end-to-side neurorrhaphy involves the application of epineurotomy or perineurotomy. Viterbo^[5] and Cao^[16] demonstrated no significant difference for end-to-side neurorrhaphy with and without epineurial window. Likewise, Viterbo *et al*^[45] revealed no difference between neurorrhaphies with and without perineurial window. These observations may, in part, be explained by the finding that the regenerating axons following end-to-side neurorrhaphy can penetrate the endoneurium, perineurium, and epineurium^[17].

According to some investigators, histologic results were better when a perineurial window was opened^[19,20]. This can be attributed to the greater degree of axonal damage to the donor nerve and subsequently the enhanced axonal regeneration after perineurotomy. When fibrin glue is used as an alternative to end-to-side neurorrhaphy, no damage to the donor nerve trunk is produced. This may explain the absence of muscle reinnervation after end-to-side coaptation with fibrin glue, without removing the epineurium^[46]. According to our studies, resection of a small part of the epineurium and placement of epineurial sutures without damaging the underlying perineurium improves the functional outcomes following terminolateral nerve repair without compromising the function of the donor nerve (Figure 2)^[44].

Clinical applications

To date, there have been no large clinical series describing either satisfactory or disappointing results after end-to-side neurorrhaphy. In 1993, Viterbo^[11] first applied end-to-side neurorrhaphy in recent clinical practice with the use of cross-facial nerve graft transplantation for the treatment of facial palsy. Reinnervation was observed in selected patients. A few years later, end-to-side neurorrhaphy was used to bridge the nerve gap after ulnar nerve injury. In this case, the median nerve was the donor nerve^[47]. The authors reported ulnar nerve motor and sensory restoration without deterioration of the donor nerve. Yüksel *et al*^[48] described a case of severe upper extremity nerve injury treated with end-to-side neurorrha-

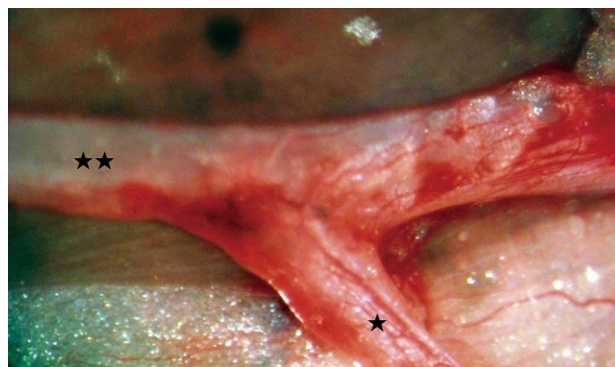


Figure 2 End-to-side neurorrhaphy between the tibial nerve (double asterisk) and the peripheral stump of the peroneal nerve (single asterisk) 90 days after surgery. Note the smooth transition from one trunk to the other resembling normal bifurcation of the tibial nerve. Also note the newly formed vessels at the outer layer of the nerve trunks traveling from the donor tibial nerve to the recipient peroneal nerve.

phy of the median and radial nerves to the ulnar nerve. The patient had satisfactory sensory recovery.

Amr *et al*^[49] reported satisfactory results in 11 cases of brachial palsy injury treated with end-to-side and side-to-side grafting neurorrhaphy. Deterioration in donor muscle motor power was observed in one case, which improved a year later. Santamaria *et al*^[50] sutured the lateral antebrachial cutaneous nerve in an end-to-side fashion to the cervical plexus, posterior auricular, or hypoglossal nerve where it was not possible to preserve the proximal stump of the lingual nerve in twenty-eight patients with tongue cancer who underwent hemiglossectomy and primary reconstruction with innervated radial forearm flaps. Sensory tests were significantly diminished when end-to-side nerve repair was used.

In digital nerve reconstruction, of 5 patients who underwent end-to-side neurorrhaphy four had sensitivity near to completely normal and one patient had a poor result^[51]. Satisfactory results in all patients were also obtained in a series of ten nerve defects at the palm or digit level treated by end-to-side neurorrhaphy. Donor nerve injury was recorded in one case^[52].

CONCLUSION

Experimental and clinical studies suggest that end-to-side neurorrhaphy can provide satisfactory functional recovery in the recipient nerve, without any deterioration of donor nerve function. The source of the regenerating axons traveling in the epineurium of the donor nerve is thought to be the proximal Ranvier's nodes at the site of end-to-side neurorrhaphy, however, histologic evidence is still lacking. Partial neurotomy of the donor nerve may enhance regeneration of motor neurons through end-to-side neurorrhaphy and reinnervation of motor targets. To date, a limited number of reported cases in clinical practice have revealed that the end-to-side technique may become a viable means of repairing peripheral nerves in certain clinical situations.

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Acknowledgments to reviewers of World Journal of Orthopedics

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Orthopedics*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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Events Calendar 2011

January 16-20, 2011
Combined 4th International
Conference of the Saudi Orthopaedic
Association & SICOT Trainee Day,
Abha, Saudi Arabia

January 24-27, 2011
7th Middle East Orthopaedics
Conference 2011, Dubai International
Convention Centre, Dubai,
Saudi Arabia

January 28-30, 2011
National Orthopedic Conference
2011, San Francisco, California,
United States

February 15-19, 2011
American Academy of Orthopaedic
Surgeons, San Diego, CA,
United States

February 16-20, 2011
2011 Annual Meeting of the American
Academy of Orthopaedic Surgeons,
San Diego, CA, United States

February 19, 2011
Pediatric Orthopaedic Society of
North America Specialty Day, San
Diego, CA, United States

March 09-11, 2011
Annual London Imperial Spine
Course, London, United Kingdom

March 21-25, 2011
31st Caribbean Orthopaedic
Meeting, Anse Marcel, Saint Martin

March 28-April 02, 2011
The Association of Children's
Prosthetic-Orthotic Clinics 2011
Annual Meeting, Park City, UT,
United States

April 01-04, 2011
Ain Shams 2nd Orthopaedic
intensive course (Orthopaedics from
A to Z), Cairo, Egypt

April 20-22, 2011
IMUKA 2011: Masterclass in
Arthroscopy and Related Surgery,
Maastricht, Netherlands

May 11-14, 2011
2011 POSNA Annual Meeting,
Montreal, Quebec, Canada

May 12-15, 2011
84th Annual Meeting of the
Japanese Orthopaedic Association,
Yokohama, Japan

May 15-19, 2011
8th Biennial ISAKOS Congress
(International Society of
Arthroscopy, Knee Surgery and
Orthopaedic Sports Medicine), Rio
de Janeiro, Brazil

May 25-28, 2011
16th Pan Arab Orthopedic
Association Congress & 27th
SOTCOT Congress, Tunis, Tunisia

June 01-04, 2011
12th EFORT Congress in cooperation
with the Danish Orthopaedic
Association (European Federation

of National Associations of
Orthopaedics and Traumatology),
Copenhagen, Denmark

June 08-12, 2011
2011 ABJS Annual Meeting
(Association of Bone and Joint
Surgeons), Dublin, Ireland

June 15-18, 2011
11th Annual Meeting of the
International Society for Computer
Assisted Orthopaedic Surgery,
London, United Kingdom

July 07-09, 2011
66th Annual Meeting of the
Canadian Orthopaedic Association,
St. John's, Newfoundland and
Labrador, Canada

July 13-16, 2011
18th International Meeting on
Advanced Spine Techniques,
Copenhagen, Denmark

July 22-24, 2011
Sri Sathya Sai International
Orthopaedic Conference- 2011
On Pelvis And Lower Extremity
Trauma", Sri Sathya Sai Institute
of Higher Medical Sciences,
Prasanthigram, Puttaparthi, Andhra
Pradesh, India

July 25-28, 2011
2011 Update in Orthopaedics, Grand
Wailea Hotel Resort & Spa, Wailea,
Maui, Hawaii, United States

September 06-09, 2011

SICOT 2011 XXV Triennial World
Congress, Prague, Czech Republic

September 13-16, 2011
BOA/IOA Combined
Meeting (British Orthopaedic
Association & Irish Orthopaedic
Association), Dublin, Ireland

September 14-17, 2011
23rd SECEC-ESSSE Congress
(European Society for Surgery of
the Shoulder and the Elbow), Lyon,
France

September 14-17, 2011
46th SRS Annual Meeting &
Course (Scoliosis Research Society),
Louisville, Kentucky, United States

September 15-18, 2011
2011 World Congress on
Osteoarthritis, San Diego, California
92167, United States

September 21-23, 2011
HIP IMPROVEMENTS AND
PROCEEDINGS, Toulouse, France

October 25-28, 2011
DKOU 2011-Deutscher Kongress
für Orthopädie und Unfallchirurgie,
Berlin, Germany

November 7-11, 2011
86ème Réunion Annuelle SOFCOT,
Paris, France

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EOA 63rd Annual International
Conference, Cairo, Egypt

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The columns in the issues of WJO will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systematically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in orthopedics; (9) Brief Articles: To briefly report the novel and innovative findings in orthopedics; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in WJO, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of orthopedics; and (13) Guidelines: To introduce consensus and guidelines reached by international and national academic authorities worldwide on the research orthopedics.

Name of journal

World Journal of Orthopedics

ISSN

ISSN 2218-5836 (online)

Indexed and Abstracted in

Digital Object Identifier and Directory of Open Access Journals

Published by

Baishideng Publishing Group Co., Limited

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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- 12 **Breedlove GK**, Schorheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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