Distraction Histogenesis: From Biology to Novel Applications 牽拉成組織技術:生物學機理和新應用

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Hong Kong: City Center



Hong Kong: City Center

the second second

Hong Kong: Buddha Mountain

坚决反对非法占"中"

跳梁小丑必败无疑!

Skeletal tissues are formed spontaneously during distraction histogenesis (DH). DH is a most cost-effective form of functional tissue engineering.



Distraction osteogenesis- History



Director, Rizzoli Orthopaedic Institute, Bologna, Italy (1899-1912)

Codivilla A. (1905) On the means of lengthening in the lower limbs, the muscles and tissues which are shortened through deformity. <u>Am. J.</u> <u>Orthop. Surg., 2:353-369.</u>

Distraction osteogenesis- History



Ilizarov, G.A. -- Tension-Stress Principles *Clin Orthop, 238 & 239, 1989*

> Mechanical stimulation can promote and maintain skeletal tissues' regenerating potentials.

Prof. G.A. Ilizarov 1921-1992

Birth place of Ilizarov Techniques The Russian Ilizarov Centre, Kurgan, Russia

September 1991, Dr. Ilizarov in Beijing 301 Hospital with Prof. Lu Shi-Bi



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Li Gang

Emergency 1st Department of Surgery The General Hospital of PLA Wu-Ke-Song Road Beijing P.R.China

Dear Dr. Li Gang,

I would like to express my gratitude for your attention to me and also for the photo you sent to me.

Please find enclosed two of my publications and Course programmes. As you know we run 10-day Courses on various problems developed at our Centre.

Please inform us which of the Course you'd like to attend and as soon as the group for the topic is formed you will be advised additionally.

Yours sincerely,

Prof. G.A.Ilizarov

AM USSR Academy of Sciences General Director All-Union Kurgan Scientific Centre for Restorative Traumatology and Orthopaedics Kurgan USSR



Dr. Ilizarov and me September, 1991, Beijing, 301 Hospital



Visiting Doctor 1993; D Phil (1994-1997); The Lord Nuffield Scholarship 1998 at Univ. Oxford



What is distraction osteogenesis (DO)







Osteomoty
External Fixation
Gradual Traction (lengthening)

The definition of the zones in the regenerate



Li, et al. JOR 1997;15:765-72.



Effect of lengthening rate on cell proliferation *Li, et al. JOR 1997; 15:765-72, 1997.*



Cell proliferation in the PMF, X 400

Cell proliferation in the NBZ, X 400

Rate:

Cell Proliferation and Apoptosis Co-exist



TUNEL in PMF



TUNEL in FZ

Rapid bone remodelling during DO is associated with apoptosis and osteoclastic activities.

Li, et al, JOR 2003; 21:94-101.

TRAP



Rate: 0.7 mm/day

TUNEL in NBZ



TEM apoptotic changes

Angiogenesis in Distraction Osteogenesis

Angiogenesis plays a key role in DO.



Angiography showing new vessels in the regenerate.

Angiogenesis study during DO



MF

B

Li, et al. J Orthop Res 1999; 17:362-7.

ଧୋ

IHC, Type IV collagen, x 400



Possible Biological Mechanisms of DO



G Li, Current Opinion in Orthopaedics, 2004; 15: 325-30.

Rat DO Model



3 weeks in consolidation period (safranin O staining, Tibia)

Primary Result of Microarray

		Groups					Up- regulated		Down- regulated		Total	
	Г	Distraction <i>vs</i>		Control			74		26		100	
۱	+	- Fracture	VS	Cont	rol		25		13		38	
		Fracture	VS	Distr	actior	า	10		56		66	
		►rno-miR-13	3b-3p	ţ	16.7	fold-cha	nge	MyoD Si R	myo DF1/C unx2	genesi XCR4 osteo	s (muscle-spe osteogenesis genesis (C2C12	ecific) s? cell line)↓
		rno-miR-134	4-5p	\uparrow	18	fold-cha	nge	brain-s	specifi	c (neu	rogenesis)	
	\rightarrow	rno-miR-45	5-3p	Ť	1.5	fold-cha	nge	Sall1	VEC	GF-A (a	ngiogenesis))



No stretching

Stretch at 8% Strain, 30 circles / min, 4h

In vitro tensile loading to promote tendogenic differentiation (unpublished data)







OA model

牵拉关节治疗关节炎



OA+ non-Distraction OA+ Distraction

牵拉关节治疗关节炎

Joint distraction significantly reduced subchondral bone density and reduced inflammatory cytokines.







Enhancement Bone Formation During DO Physical stimulation **Physical stimulation** Weight-bearing exercise <u>Ultrasound</u> LIPUS-20min Control LIPUS-40min LIPUS LIPUS LIPUS LIPUS

Chan, et al. Dose-depent effect of low-intensity pulsed ultrasound on callus formation during rapid DO. J Orthop Res 2006; 24:2072–9.

Enhancement Bone Formation During DO

- Molecular Therapy •rhBMP-2
- A latency period 7 days
- Tibiae lengthened 2 cm over a period of 10 days
- Rate: 2 mm/day
- Rhythm: 2 increments/day
- rhBMP-2 (75 µg) was administrated to the gap
- Placebo controls

Li, et al. rhBMP-2 in Distraction Osteogenesis. JOR 2002; 20: 658-67.



Thrombin-related peptide TP508 enhanced bone consolidation

TP508 300 μg injection twice

Dextran gel Inject Control

Dextran gel with microspheres 300 µg TP508 injection once



Novel application of HA-TCP biomaterials in distraction osteogenesis shortened the lengthening time and promoted bone consolidation



Day 0 Day 12 Day 17 Day 27 Day 37

Journal of Orthopaedic Research 2009



Distraction Osteogensis with Biomaterials













New Clinical Applications of **Distraction Osteogenesis Techniques** Larger bone defect correction Cosmetic lengthening Spine deformity correction Vascular diseases management • Others...

患儿因患骨髓炎致骨坏死、骨外露 骨缺损,经骨外固定治疗2年而愈。

Large Bone defect (20 cm) during to osteomyelitis











External skeletal





Beijing Institute of External skeletal Fixation Technology http://www.esf.org.cn







Beijing Institute of External skeletal Fixation Technology http://www.esf.org.cn Clinical Outcome Limb-reconstruction

肢体延长术矫治下肢特大幅度短缩畸形

患者: 女、16岁, 左股骨胫骨多发性内生性骨软骨瘤, 致下肢短缩 30.5cm (A2)。同期进行股骨和胫骨延长, 恢复正常肢体长度, 经过顺利。



Case Report and Retrospective Studies /Analysis for more than 1,500 cases in Beijing. Planned publications in N. Eng. J. Medicine; Lancet; Science-Translational Medicine, JBJS, etc.



Case 1

Male. 21 years, height 1.20 m $_{\odot}$ bilateral tibial lengthening for 18 cm.

图注: 1、术前外观 2、2-4延长中x-线情况,5完成治疗的X-线情况。









After First Treatment 18 cm tibial lengthening

Before Treatment







After 2nd 8 cm femoral lengthening

Barcelona, Word Congress of External Fixation and ASAMI International Meeting, 20-22 October 2010

2010/10/21 01:11

РОССИЙСКИЙ НАУЧНЫЙ ЦЕНТР «восстановительная травматология и ортопель имени академика г.а. илизарова

2006 October, the Frist Delegation from PR China to visit Russian Kurgan Ilizarov Centre, Drs. Li G, Qin SH and Xia HT.

New Clinical Applications of DO Spine Deformity Correction

Photograph taken at Russian Kurgan Ilizarov Centre, with permission, by Dr. G Li

New Clinical Applications of DO Hip Deformity Correction

Photograph taken at Russian Kurgan Ilizarov Centre, with permission, by Dr. G Li



29/09/2013 10⁻⁵³

Prof. Gang Li, Visited Russian Ilizarov Centre, Kurgan, October 2006

New Clinical Applications of DO Treatment of Cerebrovascular Disease / Stroke





Photograph taken at Russian Kurgan Ilizarov Centre, with permission, Prof. G Li



Apply skull distraction above the stoked areas will enhance blood supply and lead to rapid functional recovery.

Neurosurgeons need join hand with orthopaedic surgeons and engineering to explore this revolutionary, costeffective novel treatment strategy.

New Clinical Applications of DO Treatment of Peripheral Vascular Disease



Courtesy of Dr. Long Qu, Beijing Bone Lengthening and Transport Centre, China.



Ilizarov's grandson in Beijing, 2012.04



Dr. Sivetlana Ilizarov in Beijing, 2012.04





Summary: Changes of Concepts of DO

Ilizarov Era (1940s-1990s): Distraction osteogenesis; tension-stress principles; deeper understanding of the role of mechanical stimuli in skeletal tissue regeneration and repair.

Modern Era (1990s-present): Distraction histogenesis; insights of molecular, genetic and cellular mechanisms; extension of new applications into other fields for functional tissue engineering and rehabilitation.

The future: More clinical and basic research lead to new, effective and costeffective treatments for more challenging conditions and diseases. CUHK LiKS-SBS Stem Cell and Regeneration Lab Members 香港中文大学医学院-生物医学学院干细胞与再生医学组-李刚团队



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