·工作综述·

周围神经缺损修复新方法——神经延长术

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周围神经缺损在临床上常见,也是临床治疗的难点[1]。创伤性神经缺失、神经肿瘤医源性切除、神经延期修复时的神经短缩等均可导致不同程度的神经缺损[2-5],我国每年周围神经缺损患者高达30~50万例。对于小的周围神经缺损,可通过神经游离、转位、改变患肢体位和姿势等方法,将神经两断端接近后进行直接缝合[6]。对于较大的周围神经缺损,应用上述方法无法达到神经的无张力修复时,则需采用其他方法进行神经修复。目前临床上最常采用的是神经移植术[7-8],即采用自体神经段桥接缺损的神经,进而达到神经缺损修复的效果,但由于神经移植术的移植神经来源有一定的限制,且通常还要以牺牲供区神经功能为代价[9-10],因此寻找其他修复方法和技术一直是周围神经缺损研究领域的热点。

我们从肢体延长手术中获得启示:周围神经的特殊组织结构及力学性质使得神经干具有一定限度的抗张性,一定范围内延长神经不会对神经造成损伤。经过延长神经可以使神经断端长度得到增加,从而达到缩短神经缺损距离的目的,使得缺损的神经能够直接缝合修复,因此我们开展了用周围神经延长技术修复周围神经缺损的系统研究:完成了周围神经延长器研发、周围神经延长极限、延长神经修复神经缺损效果等多个研究,现将此系统性研究成果报道如下。

1 适合周围神经缓慢均匀延长的周围神经延长器

最初的神经延长是通过对延长神经断端进行简单机械拉伸,这种方法易造成神经损伤,而且延长后的神经也易产生回缩[6]。随后,有学者采用皮肤或软组织扩张器对神经进行延长,虽然能够达到延长神经的效果,但其在延长神经的有效固定、神经延长的精确量化方面存在不足[11-12]。针对上述缺陷,我们设计研发了周围神经延长器,延长器采用球囊结构对神经干进行均匀延长,通过向球囊注水使球囊扩张,进而利用球囊扩张的张力使固定于球囊表面的待延长神经获得均匀延长。这种延长一方面避免了简单的机械牵拉造成的神经损伤,更重要的一方面是可以完成多次、缓慢、均匀的延长,从而有效达到用神经自体延长的长度修复断端缺损的目的。我们研发的周围神经延长器获得多项国家专利,有望近期获得医疗器械准入批件,成为临床产品。

2 周围神经的可延长性及神经缺损修复范围

2.1 周围神经对快速/缓慢延长的耐受性

首先,我们研究了周围神经对单次快速延长的耐受性。通过动物实验证实,在单次快速延长时,神经在10%延长率内耐受性较好,当延长率超过20%时将会对延长神经造成不可逆的损伤。随后,我们在周围神经慢性延长耐受性的研究中发现,当进行缓慢神经延长(延长速度 1 mm/d)时,神经在27.0%延长率内耐受性较好,延长率超过37.5%时可导致对延长神经不可逆的损伤[11-12]。上述研究结果表明周围神经对慢性延长的耐受性远优于一次性的急性延长,对于较小的神经缺损可以采用单次快速延长,而对于较大的神经缺损,则可采用慢性延长[11-12]。

2.2 近端神经和远端神经的延长极限及神经缺损修复范围

上述周围神经延长耐受性的研究结果提示修复

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过程中近端和远端神经均可进行延长，但在神经修复后的再生过程中，近、远端神经的病理生理过程却是完全不同的[10]，由此推断近端和远端神经在对神经延长的耐受性上可能存在差异，而近、远端神经可延长的极限，决定了神经延长修复神经缺损的可修复范围，为此我们对近端神经和远端神经的延长极限及神经缺损修复范围进行了系统的研究。在近、远端神经的单次快速延长耐受极限的研究中，我们发现近端神经单次快速延长率极限为 10.0%，而远端神经单次快速延长率极限为 20.0%，由此明确了周围神经损伤后采用单次快速神经延长技术可以修复神经缺损的最大长度 = 近端神经长度的 10.0% + 远端神经长度的 20.0%[11-12]。在近、远端神经的多次缓慢延长耐受极限的研究中，我们发现近端神经多次缓慢延长率极限为 18.4%，远端神经神经多次缓慢延长率极限可达 52.0%，因此我们认为周围神经损伤后采用多次缓慢神经延长技术可以修复神经缺损的最大长度 = 近端神经长度的 18.4% + 远端神经长度的 52.0%[11-13]。

3 周围神经延长的组织学基础及病理生理学变化规律

在系统完成周围神经单次及多次延长极限的基础上，我们采用组织学染色、免疫组织化学染色以及单根神经纤维剥离技术对周围神经延长过程中神经干组织的病理生理学变化特点进行研究，发现方塔纳带(Fontana)是决定周围神经单次延长极限的重要结构基础[13]；当神经延长幅度达到 10% 时，神经干内方塔纳带结构消失，郎飞结(nodes of Ranvier)、施-兰切迹(Schmidt-Lantermann incisure)等增宽，但无轴索及髓鞘的断裂；当神经单次延长幅度达到 20% 时，出现神经轴索及郎飞结的断裂，同时神经延长过程中的神经电生理检测结果与这一病理生理学过程相符[13-17]。

4 周围神经延长和神经移植

自体神经移植一直被认为是临床周围神经缺损修复治疗的金标准，我们在动物实验中，对比研究了周围神经延长与自体神经移植修复周围神经缺损的效果，证实一定范围的延长神经修复神经缺损能够取得与自体神经移植等效的修复效果[11-13]。

在此研究基础上，我们开展了神经延长修复神经缺损的临床研究，采用术中延长器对 13 例神经缺损患者进行远端神经延长的治疗，临床应用结果表明，在 4 cm 的缺损范围内，延长的神经能够填补缺损范围，所有的患者神经均可进行无张力缝合。通过对患者进行系统的随访证实，患者神经修复后，受损神经再生良好，可达到同类型无缺损神经损伤患者的修复效果[18]。对比性研究证实神经延长技术可用于临床周围神经缺损的修复，并在一定程度上可以替代神经移植技术，成为临床应用的新方法。

5 总结与展望

上述系列实验研究解释了周围神经自身可延长性的生物现象，并清楚的记录了其延长过程中的特定变化及极限，证实神经延长技术可以取得传统的神经移植修复周围神经缺损的修复效果，并具有如下优点：采用神经自体延长，无需神经移植和人工神经，因此不受自体神经取材限制，无需牺牲供区神经功能；无人工神经机体免疫排斥反应，神经再生效果优于人工神经移植；外科操作方便，延长后神经可进行直接外膜缝合，容易被外科医师接受，将会成为神经缺损修复的创新性治疗技术[19-20]。

周围神经延长技术修复周围神经缺损的效果已经得到初步验证，但真正的临床广泛应用仍有诸多工作需要开展。后续研究中，一方面我们将通过专利转化促进神经延长器的产业化，获得国家医疗器械的正式批件；另一方面，我们开展更加广泛的应用周围神经延长修复周围神经损伤的临床研究，进一步对其在周围神经损伤修复中的效果进行验证。

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New treatment for peripheral nerve defects: nerve elongation

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SUMMARY Peripheral nerve defects are still a major challenge in clinical practice, and the most commonly used method of treatment for peripheral nerve defects is nerve transplantation, which has certain limitations and shortcomings, so new repair methods and techniques are needed. The peripheral nerve is elongated in limb lengthening surgery without injury, from which we got inspirations and proposed a new method to repair peripheral nerve defects: peripheral nerve elongation. The peripheral nerve could be elongated by a certain percent, but the physiological change and the maximum elongation range were still unknown. This study discussed the endurance, the physiological and pathological change of peripheral nerve elongation in detail, and got a lot of useful data. First, we developed peripheral nerve extender which could match the slow and even extension of peripheral nerve. Then, our animal experiment result confirmed that the peripheral nerve had better endurance for chronic elongation than that of acute elongation and cleared the extensibility of peripheral nerve and the range of repair for peripheral nerve defects. Our result also revealed the histological basis and changed the rule for pathological physiology of peripheral nerve elongation: the most important structure foundation of peripheral nerve elongation was Fontana band, which was the coiling of nerve fibers under the epineurium, so peripheral nerve could be stretched for 8.5% -10.0% without injury because of the Fontana band. We confirmed that peripheral nerve extending technology could have the same repair effect as traditional nerve transplantation through animal experiments. Finally, we compared the clinical outcomes between nerve elongation and performance of the conventional method in the repair of short-distance transection injuries in human elbows, and the post-operative follow-up results demonstrated that early neurological function recovery was better in the nerve elongation group than in the conventional group. On the whole, all of these experimental results revealed the physiological phenomenon of peripheral nerve elongation, and described the physiological change and stretch range in detail. The systematic research results have filled the blank in this field, which is very helpful for clinical limb lengthening surgery, the design of elongation surgery and the evaluation of the peripheral nerve stretch injury. Peripheral nerve elongation will become an innovative treatment technology in repairing peripheral nerve defects.

KEY WORDS Peripheral nerves; Nerve elongation; Nerve Defect; Repair