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Bladder Re-Innervation—State of the Art

Chuan-Guo Xiao¹

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Abstract Neurogenic bladder used to have no cure. An old idea of bladder re-innervation resurfaced with this new concept and promising results. This article reviews the current status of the clinical studies on bladder re-innervation with a somatic-autonomic reflex arc (Xiao procedure). A total of 2840 patients to date with spinal cord injury or spina bifida underwent the Xiao procedure for neurogenic bladder in three major medical centers in China. The effective rates have been stable in the range of 67~85 %. While four centers in USA carried out clinical trials of the Xiao procedure, three reported positive results similar to the Chinese results, but one reported 100 % failure. Two centers in Denmark and Germany also reported negative responses of SCI patients to the Xiao procedure. By comparing the patient's information in different countries and different centers, a few major facts affecting the results have been identified. These include overextension and fibrosis of detrusor muscle, as well as incorrect anticholinergic and CIC usage. A list of criteria has been suggested to maximize the effect of the Xiao procedure.

Keywords Xiao procedure · Neurogenic bladder · Bladder re-innervation

Introduction

Neurogenic bladder can be caused by many diseases as well as trauma and has been a major challenge to many subspecialties of medicine as well as to a vast population of patients and their

families. Though CIC and anticholinergics improved daily management of the bladder, no substantial breakthrough in the treatment of neurogenic bladder have been reported until the end of the last century. An old idea of bladder re-innervation resurfaced with very promising results. This article will review current status of bladder re-innervation in SCI and spina bifida patients, represented by a somatic-autonomic re-innervation procedure (Xiao procedure).

Xiao reported success of a somatic-autonomic reflex pathway procedure (Xiao procedure) for neurogenic bladder to gain voluntary control and voiding in animals [1–3], then in 15 patients with spinal cord injury (SCI) [4], and then 20 children with spina bifida [5]. The difference of the Xiao procedure from prior attempts at bladder re-innervation was that the motor axons of a somatic reflex arc were used to regenerate into autonomic preganglionic nerves, thus, re-innervating bladder parasympathetic ganglion cells and, thereby, transferring somatic reflex activity to the bladder smooth muscle. Since then, many basic and clinical investigators have reported their studies on somatic re-innervation of the bladder. Many very inclusive articles have reviewed the history, methods, and progress of bladder re-innervation extensively [6, 7, 8]. This article will focus on the most recent year's clinical results of the Xiao procedure after our reports of success in restoring bladder and bowel control in SCI and spina bifida patients, and then analyze the reasons for success or failure, and to suggest a simplified guideline to maximize the efficacy of the somatic-autonomic bladder re-innervation procedure.

Results of Bladder Re-Innervation With the Xiao Procedure in SCI Patients

Besides Xiao's team and their hospitals, there are two more major centers in China working on bladder re-innervation.

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Since 2008, Hou CL's team in the Second Army Medical University of China has been working on somatic-autonomic re-innervation for neurogenic bladder caused by SCI. They published the results of a confirmatory clinical study in 2009 independently, using a slight variation on the Xiao procedure. They chose the S1 nerve root instead of the L5 root to enable initiation of the somatic-CNS-autonomic reflex by tapping on the Achilles tendon in addition to skin stimulation, creating an Achilles tendon-to-bladder reflex pathway. Nine of 12 paraplegic patients (75 %) with hyper-reflexic neurogenic bladder and detrusor-EUS dyssynergia caused by complete suprasacral SCI regained bladder control within 6–12 months after surgery. The procedure eliminated detrusor-sphincter dyssynergia and increased bladder capacity documented by urodynamic testing 1 year after surgery [9•]. They also tried T11 ventral root to S3 ventral root for atonic bladder after conus medullaris injury and reported similar success except longer regenerating time of 2 years postoperatively. Hou's team in the Second Army Medical University ChangZheng Hospital have performed the somatic-autonomic re-innervation procedure for more than 400 SCI patients with an effective rate about 70 % by questionnaires [10, 11]. While more than 30 hospitals in China are performing the Xiao procedure routinely for neurogenic bladder after SCI, Chao XJ's team in Nanjing Medical University modified the Xiao procedure by extradural S1 to S2 ventral root anastomosis with shorter OR time and post surgery regeneration distance and fewer complications such as spinal fluid leaking and headache [12, 13]. They have also reported a very interesting study on “an acetyl cholinesterase antibody-based quartz crystal microbalance for the rapid identification of spinal ventral and dorsal roots,” [14] which may replace the current methods of intro OR electrophysiological monitoring [15], to revolutionize and simplify the critical root identification process for more accurate anastomosis.

There were similar success reports in USA. A NIH-supported clinical trial was carried out at the NYU Medical Center using the Xiao procedure for neurogenic bladder caused by complete SCI. The positive results confirmed the principle of somatic-autonomic re-innervation [16]. Patwardhan reported a 6-year-old girl with neurogenic bladder caused by gunshot SCI, who was cured by the Xiao procedure and regained voluntary voiding 5 months post surgery [17].

Tuite and colleagues [18] performed the Xiao procedure in a 10-year-old boy with chronic T10–T11 paraplegia, but failed to reproduce effective results. When a separate lumbosacral intradural procedure was performed 3 years later, the previous L5 to S2–S3 anastomosis was found to be anatomically intact. However, nerve action potentials could not cross the repair site. Histological analysis showed neuroma formation with very little nerve growth across the repair site. The value of this case report should be in demonstrating that the Xiao

procedure, like any other neural anastomosis, may end in neuroma formation and then failure of bladder re-innervation. Neuroma formation may be one of the major causes for the failure of the Xiao procedure. The only way to correct the situation is to remove the neuroma surgically and redo the anastomosis.

However, Rasmussen and colleagues [19•] in Denmark reported complete failure on 10 of 10 SCI patients who underwent Xiao procedure. The only significant change was less leakage on urodynamic evaluation. This kind of complete failure should raise concern for underlying problems. We compared the management of neurogenic bladder caused by SCI in Europe and China. In Europe, CIC plus anticholinergics regime has been the gold standard for SCI patients since the World War II. It was effective in paralyzing the bladder, protecting the upper urinary tract, and keeping the patient dry, but frequent bladder overdistension and then detrusor decompensation and fibrosis could be unavoidable. While most SCI patients in China cannot afford the costs of CIC and anticholinergics, the condom catheter is the solution for overactive detrusor contraction and leaking, and thus ironically preserved detrusor from overdistension and fibrosis in most SCI patients [4, 9•]. When a clinical trial of the Xiao procedure supported by the NIH was carried out in New York University Medical Center, we realized the conflict between anticholinergics and neural re-innervation of bladder, and then the criteria for the Xiao procedure were published, including cessation of anticholinergics and the less than 700 ml bladder capacity [7]. However, the Denmark teams did not adopt these criteria, as they mentioned that “Although these criteria were first published after the current study began, most of them were met in our series except the upper limit of bladder capacity and the cessation of anticholinergic medication. In regard to the latter we deemed that the medication was essential for patient well-being throughout the 18-month study period.” Anticholinergics plus CIC have been the “gold standard” treatment for neurogenic bladder caused by SCI for more than half a century in developed countries. It aims to block the neural connection between postganglionic nerves and detrusor, to paralyze the detrusor, to inhibit the bladder contraction and to make the bladder a low pressure storage tank for CIC. The Xiao procedure, however, is to re-establish the neural control of lower urinary tract via the somatic-autonomic re-innervation to allow voluntary voiding. The postganglionic nerve to detrusor connection is the last and most important leg of the somatic-CNS-autonomic reflex arch, and if this leg is blocked by anticholinergics continuously, the newly established reflex arch could never be activated to initiate detrusor contraction and voiding, as the cases in these reports. This may well explain why all patients in the Denmark trial failed. It is also impossible to re-innervate and activate the bladder with huge capacity caused by overdistention and fibrosis.

Results of Bladder Re-Innervation in Spina Bifida Patients

Peters and his colleagues at Beaumont Hospital reported the US pilot study of the Xiao procedure for spina bifida children with neurogenic bladder. Of 13 subjects (nine female, median age 8 years), 3 voided small amounts of 20 cc at baseline, 1 voided 200 cc (voiding efficiency 32 %), 4 reported normal bowels, and 2 were continent of stool. Over 3 years, renal function remained stable and mean maximum cystometric capacity (MCC) increased ($p = 0.0135$). In the 10 that returned at 3 years, 8 were treatment responders with voiding efficiency >50 % and 9 had discontinued anti-muscarinics. Only 2/8 with baseline neurogenic detrusor overactivity (NDO) still had NDO, all 3 with compliance <10 ml/cm H₂O had normalized, 7/10 considered their bowels normal, 5/10 were continent of stool, and 8/10 would undergo the procedure again. The pilot study demonstrated that somatic bladder re-innervation by the Xiao procedure is also feasible and effective in spina bifida patients and can improve their elimination [20, 21•, 22].

This pilot study marked an important step for bladder re-innervation progress. It reproduced the main results statistically and proved the feasibility and efficacy of the Xiao procedure in a highly credited institution in USA. Although the effective rate was lower than what was reported by Xiao and his colleagues in China, there were reasons for it. First, three subjects that had intrauterine closure should not be enrolled in the pilot trial because their lumbar and sacral neural roots were almost completely destroyed and no good quality root could be found for anastomosis. Second, CIC and anticholinergics were not stopped as requested, till 2 years postoperatively, which may delay mature and coordination of the re-innervated bladder and urethra.

However, in total contrary to previous reported good results, Tuite and his colleagues [23] published an article titled “Lack of efficacy of an intradural somatic-to-autonomic nerve anastomosis (Xiao procedure) for bladder control in children with results of a prospective, randomized, double-blind study.” In short, they recruited 20 spina bifida kids, 10 had cord de-tethering surgery and 10 had cord de-tethering plus the Xiao procedure, in a “double-blind” study. They found out in 3 years follow-up that none of the 20 kids had any improvement in bladder function.

Unfortunately, there are some concerns about the study design and methods. It has been under strong objection from the inventor of the Xiao procedure from the first day the study started in 2009. First, the Xiao procedure had been proven to be very effective by many centers with a thousand cases and formal publications, including those in the USA: Beaumont Hospital, NYU Medical Center, and Louisiana State University. Randomized, double-blinded study requires the strictest methodology and rigorous quality control. While in the Tuite’s trial, in addition to introducing another variable-de-

tethering surgery as control, there was considerable variation in the underlying neurologic conditions and past surgical history; each of the four neurosurgeons who performed the procedure had different levels of experience. The major methodology defect was that children who had the Xiao procedure had to stop CIC and anticholinergics 3 months postoperatively, to allow regenerated axons to work with the bladder and urethra, while children who did not have the Xiao procedure should still keep using CIC and anticholinergics as guideline indicated to protect the upper urinary system. How could you manage this dilemma in a double-blind trial for 3 years? The authors tried to smooth up the defect by stating in the article twice “CIC and the use of BAMs (Bladder Active Medicines, anticholinergics) were terminated 2 weeks prior to preoperative evaluations, and most patients were able to refrain from both of these modalities for the entire 3-year follow-up.” This statement destroyed completely the scientific and methodological ground of this so-called double-blind study: Post care must be strictly the same, i.e., either all use CIC and same dosage BAMs, or all do not use CIC and BAMs. How many was the “most,” 11? 15? Or 18? Authors did not report this critical and most important data. But nevertheless, it was fundamentally wrong to continue anticholinergic medications in some and not in others, effectively not treating the other arm equally in a double-blind trial.

Inconsistent use of anticholinergic medications and CIC may be rooted in reluctance by investigators and clinicians to deviate from the accepted standard of care in the USA and Europe, which dictates CIC and anticholinergic medications for all patients with neurogenic bladder and urinary retention.

I would also quote again from Denmark report regarding anticholinergics in the Xiao procedure, to show how urologists deal with anticholinergics seriously in USA and Europe: “Although these criteria were first published after the current study began, most of them were met in our series except the upper limit of bladder capacity and the cessation of anticholinergic medication. In regard to the latter we deemed that the medication was essential for patient well-being throughout the 18-month study period”.

It seemed to be the similar situation with Tuite’s trial patients: They were scattered over different states under care of their local primary care doctors who could resist stopping anticholinergics and CIC for 3 years. So I would suggest the authors collect data from these children’s local doctors and provide more detailed data regarding the post-operative usage of CIC and anticholinergics in 3 years.

The article, however, is not the end of Tuite’s trial. Some positive results can come of it, to some degree. My suggestion is:

- (1) Since it has been out of double-blind, please let the 10 children who underwent the Xiao procedure wear a diaper and stop anticholinergics and let them try to void by push, leak, or whatever means for 2 months, then see

what happens. Giving the neurosurgeons a 50 % learning curve deduction, it should still have at least 3~4 children who will be able to void voluntarily without incontinence and CIC. All spina bifida kids after the Xiao procedure do not need scratch to void. For about 3000 kids who had the Xiao procedure, none of them needs bladder augmentation.

- (2) I built a hospital 5 years ago with 300 beds, 30 beds have been dedicated to help SCI and spina bifida patients for the Xiao procedure in connection with three major charity organizations for disabled children in China. The Xiao procedure was performed for about 200 patients per year with spina bifida or SCI. All patients for the Xiao procedure only pay 8000USD or less for all costs, or free for many poor people. The hospital has an open policy regarding the Xiao procedure patients: "If the patient cannot void voluntarily within one year (for child) or 18 months (for adult) post Xiao procedure, Prof. Xiao will redo the procedure himself for free, no matter where and who did the Xiao procedure." Now, I would like to extend this policy internationally. I will redo the Xiao procedure free for all children failed in Tuite's trial, including those who served as control. I am confident that 80 % of the kids will gain bladder and bowel control and voluntary voiding within a year, or at least as good as Peters' trial results. It may be better than 80 %, but I have to be cautious due to the fact that they had had intradural neurosurgery at least two times on the same location.

Xiao's team welcomes interested urologists and neurosurgeons to visit China, work with the Xiao procedure for 10 cases, and to follow up as many post-operative spina bifida kids as you wish. It is now as effective, safe, reliable, and simple as a hernia repair for us to restore bladder function, and voluntary voiding for the great majority of spina bifida kids and SCI patients with the Xiao procedure, as long as the crossover anastomosis is satisfactory, CIC and anticholinergics are stopped from the third month after surgery, and the bladder has no detrusor de-compensation or fibrosis.

Conclusion

In conclusion, the Xiao procedure is effective, safe, and reliable in treatment of neurogenic bladder for SCI and spina bifida patients. Understanding the procedure is important, and following the guidelines of the Xiao procedure is critical for satisfactory results.

Compliance with Ethical Standards

Conflict of Interest Dr. Xiao has no conflicts of interests to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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