Title	A randomized double-blinded clinical trial to evaluate the safety and efficacy of a novel superelastic nickel–titanium spinal rod in adolescent idiopathic scoliosis: 5-year follow-up
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A Randomized Double-Blinded Clinical Trial to Evaluate the Safety and Efficacy of a Novel Super-Elastic Nickel-Titanium Spinal Rod in Adolescent Idiopathic Scoliosis – 5 year follow-up

ABSTRACT

Purpose: To evaluate the safety and efficacy of a super-elastic shape-memory alloy (SNT) rod in treatment of adolescent idiopathic scoliosis (AIS).

Methods: Patients with AIS Lenke 1 curves undergoing fusion surgery were randomized (1:1) at the time of surgery to receive either the SNT or a conventional titanium alloy (CTA) rod. Radiographs were obtained preoperative and postoperatively up to 5 years follow-up. Parameters assessed included coronal and sagittal Cobb angles, overall truncal and shoulder balance. Sagittal profiles were subcategorized into Types A (<20°), B (20-40°) and C (>40°).

Results: Twenty-four patients with mean age of 15 years were recruited. A total of 87.0% of subjects were followed-up till postoperative 5-years but all patients had minimum 2-years follow-up. The fulcrum-bending correction index for the SNT group was 113% at postoperative day 4 and 127% at half-year while the CTA group was 112% at postoperative day 4 and only 106% at half-year. In terms of sagittal profile, the SNT group moved towards type B profile at half-year follow-up with a mean correction of 7.6° while no significant change was observed in the CTA group (-0.7°). Nickel levels remained normal and there were no complications.

Conclusions: This is the first randomized clinical trial of a novel SNT rod for treating patients with AIS, noting it to be safe and has potential to gradually correct scoliosis over time. This study serves as a pilot and platform to properly power future large-scale studies to demonstrate efficacy and superiority.

Keywords: Adolescent idiopathic scoliosis; super-elastic; nickel; titanium; rod

Introduction

The aim of spinal surgery for adolescent idiopathic scoliosis (AIS) is to correct the deformity, obtain a balanced spine and prevent curve deterioration.[1] Posterior instrumentation utilizes a combination of screws, hooks or wires with rod constructs for deformity correction.[2] No difference in correction rates have been demonstrated between different instrumentation strategies.[2] However, up to 2-10% of subjects may have experienced loss of correction postoperatively.[3-6] Risk factors for loss of correction over time can be contributed to large magnitude curves and apical translation. This phenomenon may be contributed to tissue viscoelasticity.[7-11]

Viscoelasticity is a time-dependent phenomenon. Correction forces applied by instrumentation reduce over time as the tissues relax, leading to some recurrence of the deformity. In an attempt to achieve better correction, higher corrective forces are generally applied intraoperatively and with the use of more bone anchors to share out such forces. However, high correctional forces has potential to plastically deform rods and cause screw pullout or pedicle fracture.[2] Thus, the current trend in AIS correction surgery is to use higher implant density with stiff rod constructs like Cobalt-Chromium or stainless steel. In theory, these rods should be able to positively influence the coronal and sagittal plane correction. Nevertheless, this is based mainly on biomechanical studies[12,13], whereas clinical results yield insufficient evidence in regards to correction in the coronal plane[14-16] or the sagittal plane.[17,18] In addition, due to the increased forces generated by the stiffer rods, higher density screws are required to dissipate the forces more evenly.[18-20]

Sagittal alignment has gained significant attention in recent years. Decreased thoracic

kyphosis can lead to increased risk of adjacent segment disease and poorer quality of life.[21,22] As thoracic hypokyphosis is a main feature of most AIS patients with Lenke 1 curves[23,24], there is increasing interest to correct the sagittal alignment. However, the current approach towards AIS correction may not be effective in achieving this outcome. Postoperative hypokyphosis has been associated with increased screw density. This has been attributed to different corrective maneuvers such as direct vertebral rotation.[25-28] More pedicle screws increase the overall cost of the surgery[8,19] and neurological risks related to malpositioning.[29-31]

The viscoelastic relaxation of spinal tissues may be overcome by applying a progressive and constant correction force resulting in further deformity correction after rod implantation. The force required to obtain this progressive correction is likely to be less than the force applied using current instrumentation and hence avoid the risks associated with stiff rods. As a result, perhaps fewer anchors can be used to reach the same end-point. Nickel-titanium (NiTi) alloy is a metal that has the ability to return to a previously defined shape when subjected to thermal treatment (shape-memory effect). A lesser utilized property is its super-elasticity. This is a property whereby regardless of the strain or deformation placed on the rod, the rod exerts the same recovery force, thereby making it predictable and ideal for use in scoliosis patients, as curve magnitude varies. Thus, it can provide a predictable recovery force regardless of the severity of the spinal deformity. The authors have developed such a new super-elastic nickel-titanium spinal rod (SNT) with maximal superplastic properties at human body temperature.[32] Moreover, when the rod is cooled to below 20°C, it has a low yield strength and can be deformed easily into the shape of the spinal deformity, making surgical insertion easy. Then when the rod is warmed to human body temperature (37°C), the rod becomes maximally super-elastic and will attempt to return to its pre-designed contour. We have made a 6.0mm spinal rod, which under

laboratory conditions can produce 300N recovery force in bending and torsion. This force can be tailored to requirements by heat treatment processing, but our preliminary *in-vivo* study suggest that a 300N force should be sufficient to result in curve correction in our patient population (unpublished data). The time it takes for the rod to return to its initial shape, will depend on the stiffness of the spine. *In-vivo* goat studies performed in our laboratory, suggest that maximal recovery of the rod occurs by 3-4 weeks and should not affect fusion process. These goat experiments were not published but it is important to note that deformity was observed immediately and progression of deformity up to one week postoperatively after implantation of pre-contoured superelastic rods.

Although nickel alloys are commonly used in implant materials, the high proportion of nickel present in the SNT rod, raises potential concerns with allergic reactions or even toxicities in humans.[33] To enhance its safety profile, the rods undergo a surface treatment process called plasma immersion ion implantation, whereby a layer of titanium nitride (TiN) is formed on the surface making the rod more mechanically durable and reduces the chance of nickel release into the blood stream [30, 36-38]. The safety and efficacy of this surface modified spinal rod has been established in *in-vitro* and animal studies with rabbit and goat models[34-43].

This is the first randomized controlled human clinical trial that addresses the safety and efficacy of a surface treated SNT rod in comparison to a conventional titanium alloy rod (CTA) for correction of deformity in AIS subjects.

Methods

Study Design, subject recruitment and randomization

This was a prospective parallel randomized, controlled double-blinded pilot clinical trial conducted at a single center. Institutional review board approval was acquired and informed consent was obtained by all participants in this study. Inclusion criteria included female or male of less than 25 years of age, thoracic or thoracolumbar curve, single spinal curve of >45° requiring selective thoracic fusion and those with more than 2-years follow-up. Exclusion criteria included subjects with stiff curves and a residual curve on fulcrum bending of ≥40°, having more than one curve that needs fusion, received any previous spinal surgery, known and skin tested allergy to nickel (Ni) or other implant materials. Stiff curves were excluded as this was the first trial of the SNT rods and we wanted the proof of principle to be tested in flexible curves first. Eligible patients with AIS and Lenke 1 curves were randomized at the time of surgery into two groups, to receive either SNT rods (treatment group) or CTA rods (control group).

The Clinical Trials Centre (CTC) at the University of Hong Kong (HKU) was involved in monitoring the study (reference no. CTC 0484). Block randomization by computer program was performed by a statistician in the Medical Statistics Department of the CTC. The randomization involved allocating trial subjects in equal proportion (1:1 ratio) to each of the two treatment groups. This randomizer was not involved in subject recruitment, conduct of the study, data management and statistical analysis. No other study personnel had access to the randomization list. Investigators were required to submit the trial subjects' particulars to the randomizer for assigning the trial treatment.

For the blinding details, both patients and assessors of collected data were blinded to the

rod material used. The rod material used was not disclosed to the patients until 2 years after the surgery. Surgeons were not informed of the rod material used until immediately prior to surgery, thus at the time of patient recruitment, the surgeon was not influenced by the rod material during consent for surgery. All subsequent follow-up assessments were performed by assessors without knowledge of the rod material up to the 5-year follow-up.

Intervention

The rods were made of NiTi (Ti-50.8at% Ni; Nitinol Device Company, Fremont, U.S.A) with a customized heat treatment protocol.[38] As SNT rods are super-elastic, they cannot be manually contoured during surgery. For the purposes of this study, the rods were prebent in the factory to 30° kyphosis in the thoracic portion and 30° lordosis in the lumbar portion. This was based on suggested "normal" values[44] of sagittal contour and to avoid over-aggressive sagittal correction. Variable contouring was possible depending on need. Different lengths of rods were available depending on the size of the patient, and the rods were then cut to the appropriate length to fit a specific region of the spine. The rods used in the control group (CTA) was a conventional titanium alloy (Universal Spinal System, USS; Synthes® Inc, USA). To ensure that they were contoured appropriately, an intraoperative template was used to ensure curvatures created were the same as those of the factory pre-bent SNT rods. The screws and anchors for both the control and the study group were the same (Synthes® Inc, USA), the titanium (Ti) cables were manufactured by Medtronic®, USA.

Surgical procedures were standardized regardless of the rod material. Standard posterior spinal exposure appropriate for the length of thoracic curve to be instrumented was performed

based on fulcrum-bending radiographs.[45-49]. If possible, pedicle screws were applied to the upper and lower instrumented vertebra and the one adjacent vertebrae, thus a total of 4 screws were used at both ends. In order to allow continued correction after surgery, 4 sub-laminar titanium cables were used at the intermediate levels. During surgery, the rods were inserted into the anchors using the same techniques as traditional rods. In all patients, the concave rod was inserted first and then rotated to correct the curvature. Then all screws were tightly locked. However, with the SNT rods, because they were more elastic, we found that the rod often bent back into the curvature more, but with warming of the patient to body temperature, rod shape recovery could be seen. No osteotomies were performed in either group except for our usual method of removing the inferior articular processes of intermediate facet joints for interfacet fusion.

Outcome Assessments

After recruitment, all subjects had an initial preoperative clinical and radiological assessment which included standing anteroposterior (AP) and lateral radiographs and fulcrum-bending radiographs.[46,48] Subsequent assessment intervals were made postoperatively on the first day after patient was able to stand after the surgery (usually day 1-4) and day 7. Further assessments were made on postoperative 4 weeks, 12 weeks and 24 weeks, and postoperative 1 year, 2 years and 5 years. All parameters were collected on the radiographs using the DICOM based Radworks 5.1 (Applicare Medical Imaging BV, Zeist, The Netherlands) computer software program.

The primary objective of study was to evaluate the safety and efficacy of the SNT in AIS patients. Safety was evaluated based on lack of any major intra and postoperative adverse events

that could be related to the implant. Events, such as intraoperative fracture or postoperative implant displacement and loosening, loss of scoliosis correction, neurologic deficit, failure to correct the curvature, delayed wound healing and wound infection, and Ni-related toxicity. Serum Ni levels were thus also noted.

Efficacy was evaluated by comparing SNT with CTA in achieving coronal deformity correction, using the Fulcrum Bending Correction Index (FBCI). This index is a ratio of the actual correction based on the correction rate, and the predicted correction based on the fulcrum flexibility[46,48]. It has been previously shown to allow comparison of correction between patients by taking flexibility of the curvatures into account.[2]

Secondary objectives included evaluation of sagittal deformity correction (degree of kyphosis), coronal balance (truncal shift, listing, shoulder height, clavicle angle and T1 tilt), and patient perceived outcome (SRS-22). Sagittal profiles were subcategorized into Types A (<20°), B (20-40°) and C (>40°) to define whether the kyphosis correction was hypokyphotic (A), normal (B) or hyperkyphotic (C). These were normality figures based on the proposed sagittal alignment in previous studies.[50,51] A hypokyphotic sagittal alignment usually increased and hyperkyphotic spines usually decreased in alignment.[50] Thus, the change in sagittal alignment towards normality was recorded (- if away from 20-40° and + if towards 20-40°).

Both surgeons and patients were blinded to the type of rod used prior to the surgery, and the rod material to be used was only revealed to the operating surgeon at the time of surgery. All radiographs were measured by independent observers who were also orthopaedic surgeons, but were not involved in the surgical procedure or the subsequent care of the patients. When the difference in the measurements between the two assessors was less than 5°, the mean of the two measurements were reported. When the discrepancy in the measurements between the two

assessors was more than 5°, then a consensus between the individuals was determined.

Statistical analysis

A statistician not involved with the radiographic assessment and clinical data collection performed the statistical analyses using SPSS version 19.0. Descriptive and frequency analyses were performed for all efficacy and safety parameters. All data passed Shapiro-Wilk testing for normality and Chi-square test and student t-test were performed to compare the two groups. A p-value of <0.05 was considered statistically significant.

Results

Twenty-four patients with AIS, mean age of 15 years (SD ±2.3), were recruited. One patient dropped out at the time of surgery due to lack of the correct sized rods. Thus 11 subjects (4 males, 7 females) were in the SNT group and 12 subjects (2 males, 10 females) were in the CTA group. 20 subjects (87.0%) were followed-up for a minimum of 5 years postoperatively while the remaining 3 subjects (two SNT and one CTA) were followed-up for at least 2 years postoperatively. These three patients emigrated away after the 2 year follow-up and their contact information were unable to be retrieved.

Patients in both groups were comparable as there were no statistical differences noted between the two groups in terms of clinical (**Table 1**), spine radiographic (**Table 2**) or balance (**Table 3**) parameters ($p>0.05$). Both groups had similar maintenance of the coronal Cobb angles (**Figure 1**), FBCI (**Figure 2**) and sagittal profile (**Figure 3**) postoperatively up to 5-years follow-up. However, the overall FBCI change (**Table 2**) was better for the SNT (**Figure 4**) with a steady

increase up to at least 1 month and up to 6 months postoperatively as compared with CTA (**Figure 5**).

For the sagittal profile analysis (**Table 4**), there was no significant difference in the sagittal profile from preoperatively to half-year follow-up (p=0.11). However, there were significantly more type A profiled subjects in the SNT group preoperatively and 45.5% of SNT subjects in either type A or type C preoperatively corrected to type B at half-year follow-up. This amounted to a mean change of 7.6° (±SD 9.3) towards the 20-40° range. In contrast, the CTA group had more type B profiled subjects preoperatively which reduced at postoperative half-year. Hence, only a mean change of -0.7° (±SD 13.6) towards the 20-40° range was observed in the CTA group.

Compared to the immediate postoperative result, there was a gradual change in both the coronal and sagittal Cobb angles in the SNT rods. In **Table 2**, the coronal Cobb angle at Day 4 after surgery is 20.2°, this was reduced to between 14 to 17° subsequently. While in the sagittal plane, for both SNT and CTA rods, the Cobb angles significantly increased from Day 4 postoperatively to Day 7 and subsequent follow-up. This suggested some restoration of kyphosis in both systems with time.

There was a slight increase in Ni levels (**Table 5**) postoperatively for the SNT group but returned to baseline at 6 months postoperatively and remained the same since then. There were no allergic reactions, wound complications, loss of balance, implant breakage or non-union. SRS-22 scores were similar for both groups at all intervals (**Table 6**).

Discussion

The novelty of the current study is three-fold. This is the first study that uses the super-elastic properties of a NiTi alloy to attempt to gradually correct a spinal deformity over time. Secondly, this is the first time that a novel surface treatment process is applied to the SNT rod to reduce risk of Ni reactions and enhance the mechanical and wear properties of the rod. Thirdly, it is the first randomized controlled human clinical trial with 5 years of follow-up data.

The idea of gradual deformity correction is not new, Ilizarov[52] described the techniques of gradual deformity correction of long bones using an external fixator frame, and even in spinal applications, halo-pelvic, halo-gravity tractions and internal distractions using "growing implants" have been described to gradually correct deformities over time.[53] What is novel is that we have harnessed the super-elastic properties of NiTi to allow gradual internal correction without the need for repeated surgeries or prolonged in-hospital treatment. The authors have previously demonstrated the mechanical, chemical properties and biocompatibility of the implant, as well as establishing its efficacy and safety through *in-vitro* and *in-vivo* animal studies.[37-43] Specifically, a patented technology named nitrogen plasma immersion ion implantation on nitinol surface was invented that not only suppresses nickel release from the material surface, but also enhances the surface mechanical properties.[41] It is believed that this newly modified surface is able to reduce the metal release due to mechanical fretting. The advantage and importance of harnessing super-elasticity is that the recovery force of the rod remains constant regardless of the size of the spinal deformity, thus the force is predictable and controllable, an important aspect for human use.

A clear distinction should be made between the shape-memory effect of NiTi alloys and super-elasticity. The former is in relation to change in the shape of the rod with temperature, this

has been previously used to correct the deformity instantaneously at the time of surgery[54-56], but is not so different from manual manipulation of the rod during surgery, and is unable to provide the gradual correction of deformity that is a desirable effect. While NiTi (shape-memory) rods are usually super-elastic at or above their transition temperature, conventional NiTi rods are not optimised for super-elasticity at human body temperature. We have tailor-made heat treatment processes that optimizes this, and thus these rods are fundamentally different from conventional shape-memory alloy rods.[32]

This is thus the first human clinical study using this novel spinal rod. This pilot clinical trial serves 3 main purposes. Firstly as the surface treated NiTi rods are used for the first time in human subjects, we need to demonstrate that they are safe and does not result in either a rise in the serum Ni level or any untoward side-effects; secondly, we need to demonstrate that the concept of gradual correction is possible, and that the results are at least comparable to standard techniques; and thirdly we need to have an idea of the effect size, so that we can properly power future studies.

If the flexibility of the curvatures is taken into account using the FBCI (**Table 2/Figure 2**), one is able to see a consistent trend that SNT produces a superior degree of correction, although this does not reach statistical significance. Of interest is that the SNT rod, which is very easy to bend, compared to a titanium rod, is able to produce the same degree of correction as a standard titanium rod. This can be a potential advantage for some surgeons, as the rod is much easier to manipulate intraoperatively, making rod insertion easier, and risk of implant pull-out lower. Based on this effect size, we estimate that 64 cases will be required in each arm of the study to demonstrate superiority at 2 years of follow-up ($a = 0.05$, power = 0.95). This will be the aim of future studies.

In the sagittal plane, a built-in kyphotic contour to the SNT rod can also allow continuous correction postoperatively. The thoracic sagittal profile in AIS is usually hypokyphotic, and efforts should be made during surgery to correct it. This may be common sequelae of posterior spinal fusion[26] since most consecutive all-pedicle screw constructs may lead to flatback.[8,9,57,58] In this study, there are no statistical differences between the overall sagittal alignment of the two groups. However, subgroup analysis of the different sagittal patterns show that more corrective potential is observed in the SNT group. Subjects with hypokyphosis has increases in sagittal profile while those with hyperkyphosis has decreases in sagittal profile, moving towards the more "normal" 20-40° range.[50,51] This indicates a potential to further improve the kyphosis and overall posture postoperatively. The shape-memory and super-elastic properties of NiTi contributes to this effect shown in the SNT subjects. Nevertheless, a tendency for progressive correction over time has also been observed in the CTA group. The inherent elasticity of titanium rods is likely responsible for these changes.

In terms of overall function, improvement in SRS-22 scores are observed in both groups up to 5 years follow-up. All subgroup scores improved and the rate of improvement is similar in both groups. This is a comparable finding to Carreon *et al*[59] where longitudinal cohort of 745 patients with surgical correction for AIS showed improvement in the general SRS-22 scores up to 2 years of follow-up. Comparably, the average score of 4.3 reported in her study is also similar to the findings in our study.

The main safety concern with these rods is the release of Ni after implantation. Kim *et al*[33] showed that metal ions can be detected in the serum after surgery with stainless steel rods. High levels of Ni have been noted postoperatively up to 3.8ng/ml and remains persistently elevated even at 4 years after surgery (normal: 0.3ng/ml). Similar findings can be found for Ti-

based instrumentation up to 12 months postoperatively.[60] Ni is known to be toxic to cells, can cause allergic reactions and maybe carcinogenic. However, the chemical properties of Ni is altered when formed into an alloy with Ti, drastically reducing the possibility of Ni liberation.[61] NiTi material is therefore believed to be biocompatible and have less corrosion problems because of the strong bonding between the Ni and Ti atoms, and the presence of a mainly passive Ti-oxide-based surface layer.[61-63] However, with deformity correction, there will be some unavoidable contact with the rods, which may result in the Ti-oxide layer being rubbed off. Thus to minimize the Ni safety concern even further, we have surface treated the rod with a technique called plasma immersion ion implantation.[38] The treated surface has been shown to show improved corrosion and wear resistance. Raised serum Ni can also be observed in this study but the elevated amount is well under the recommended safety limit (i.e. <10ng/mL or <170.33nmol/L).[64]. No complications arising from Ni is reported in this study suggesting that the surface-treated NiTi spinal rod is biocompatible in humans. It is also important to note that there is a baseline Ni level even in the control group as usual daily edible vegetable oils may include Ni concentrations of 0.026-0.075ug/g which poses no human health risk.[65]

This is a randomized double-blinded clinical trial based upon a novel implant for managing patients with AIS. The main limitation of the study is its small sample size. However, as this concept is new with no previous comparable studies, it is not possible to perform a sample size calculation prior to the initiation of the study. This unique study compares the safety and efficacy of the novel SNT rod to CTA rods. Thus it serves the purpose of informing us of the safety profile of the rod, and also allow us to power future studies properly. SNT rods have super-elastic properties that allows the potential to gradual correction of the deformity following surgery by a constant corrective force. Moreover, the study shows the potential of improved

sagittal correction by the SNT rods. Adequate safety and function has been observed by the absence of Ni and surgical related complications and improved SRS-22 scores. This study has successfully verified its efficacy and safety in managing AIS patients.

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Figure Legends

Figure 1: Major curve Cobb angle comparison between conventional titanium alloy rod (CTA) and super-elastic nickel-titanium alloy rod (SNT).

Figure 2: Change in Fulcrum Bending Correction Index (FBCI%) Comparison between conventional titanium alloy rod (CTA) and super-elastic nickel-titanium alloy rod (SNT).

Figure 3: Change in Sagittal Profile Comparison between conventional titanium alloy rod (CTA) and super-elastic nickel-titanium alloy rod (SNT).

Figure 4: An 18-year-old female with super-elastic nickel-titanium alloy rod implanted. Standing anteroposterior radiographs at postoperative 1 week (a) and postoperative 4 weeks (b) shows progressive correction of primary Cobb angle. Thus, there is improvement in FBCI from 116% at postoperative 1 week to 184% at postoperative 4 weeks.

Figure 5: A 17-year-old female with conventional titanium alloy rod implanted. Standing anteroposterior radiographs at postoperative 1 week (a) and postoperative 4 weeks (b) shows no further correction but even loss of correction of the primary Cobb angle. Thus, there is a reduction in FBCI from 121% at postoperative 1 week to 99% at postoperative 4 weeks.