Investigation on the Cutaneous Change Induced by Face-Lifting Monodirectional Barbed Polydioxanone Thread

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BACKGROUND Owing to its potentially greater mechanical force on the implanted tissue, barbed thread is frequently used in face-lifting procedures. However, the long-term durability thereof remains controversial. Moreover, reports on underlying histologic and molecular changes resulting from face-lifting procedures are scarce.

OBJECTIVE To evaluate histologic and molecular changes induced by absorbable, barbed face-lifting thread in an animal model.

MATERIALS AND METHODS Fragments of monofilament, monodirectionally barbed polydioxanone thread were implanted in dorsal skin from 12 guinea pigs. Tissue samples were harvested at 1, 3, and 7 months thereafter. Histopathologic analysis and quantification of Type 1 collagen and transforming growth factor beta 1 (TGF-β1) levels were performed.

RESULTS Implantation of a single fragment induced fibrous capsule around the thread. Tissue reactions were strongest at 1 month after implantation, showing marked infiltration of inflammatory cells and fibroblasts, which gradually decreased. On molecular analysis, Type 1 collagen and TGF-β1 levels were significantly increased, compared to normal skin, throughout the 7-month study period.

CONCLUSION Our results suggest that implantation of barbed thread induces strong anchorage to skin tissue. Quantitative analysis of collagen and its downstream signaling molecule TGF-β supports the long-term durability of the thread. Therefore, the authors expect potential beneficial effect for rejuvenation on its clinical application.

The authors have indicated no significant interest with commercial supporters.

The most obvious signs of aging result from chronological remodeling of underlying soft tissue structures.[1–3] While conventional nonsurgical procedures are not sufficient for improving deep wrinkles or decreased laxity, direct surgical lifting provides a sufficient mechanical force for instant and durable lifting effects. However, surgical lifting requires extensive and meticulous dissection of the superficial muscular aponeurotic system and involves a significant recovery period.[3–5] Various modifications of the technique have been introduced to simplify the procedure for both patient and the practitioner. Nowadays, thread lifting is favored as a minimally invasive alternative to surgical lifting.[6,7]

When choosing an appropriate thread material, the following qualities are decisive: enough tensile strength for tissue anchorage and durability. Showing these qualities, sutures with multiple barbs have become popular.[8,9] Their larger cross-sectional diameter and irregular shape have been proposed as inducing greater tissue reaction, and the barbs are thought to enable equal tension distribution within the dermis and subcutaneous area. A comparative study of barbed, monofilament, and multifilament threads

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ISSN: 1076-0512 • Dermatol Surg 2017;43:74–80 • DOI: 10.1097/DSS.0000000000000925

by Jang and colleagues[10] in cadaver and rat skin demonstrated strong initial tissue reactions lasting up to 4 weeks after implantation. More recently, Kurita and colleagues[11] reported that gold-coated thread shows a superior contractile profile after 7 months compared to barbed, pure gold, and gold-coated barbed threads. In both studies, histologic evaluation of animal skin revealed an early inflammatory phase with fibrous tissue development along the implanted thread. Within a few weeks, the inflammation is resolved, and the fibrous tissue showed transition to collagen and elastic fiber components.

Both absorbable and nonabsorbable suture materials are used for the thread lift procedures; however, the effectiveness of absorbable sutures is still under debate. Previous studies have tended to focus on the morphologic characteristics of suture material, and long-term data on absorbable threads are somewhat limited.[12,13] In regards to the use of absorbable thread, Savoia and colleagues[14] analyzed skin biopsy samples and ultrasonography images 2 months after thread lifting. In their study, homogenous fibrous capsule formation along the thread, as well as increases in dermal thickness and vascular structures, were noted. Meanwhile, some authors claim that the visible lifting effect achieved with absorbable thread is largely due to post-procedural edema and inflammation, which is insufficient for long-term durability.[15,16] An underlying mechanism of sustained lifting beyond original tensile strength has yet to be elucidated for absorbable thread.

Therefore, the authors aimed to evaluate histologic changes induced by absorbable thread. To do so, the authors implanted face-lifting thread in the dorsal skin of guinea pigs and analyzed subsequent tissue reactions. Additionally, the authors sought to quantify dermal molecular changes after absorbable thread implantation in an attempt to outline the actual mechanism underlying the rejuvenation effects of its application.

Materials and Methods

Barbed Sutures

In the present study, 1-0 to 2-0 USP caliber synthetic absorbable monofilament, monodirectionally barbed sutures (Youngs Lift; Y. Jacobs Medical, Seoul, Korea) were obtained from the manufacturer and are referred to as *barbed thread* hereafter. In detail, the barbs were carved at 1-mm intervals, and the thread included structures referred to as "cones" for anchorage on the advancing end. This product has been approved for use by the Ministry of Food and Drugs Safety (Korean Board of Health, Osong, Korea).

Preparation of Animals

Twelve adult Hartley guinea pigs (250–350 g; Orient Bio Inc., Seoul, Korea) were acclimated to their holding room (temperature controlled at 21 ± 1°C, 50 ± 10% humidity, and 12-hour light–dark cycle commencing at 7 AM). A standard guinea pig diet (7006 Teklad Guinea Pig Diet; Harlan Laboratories, Envigo, Seoul, Korea) and drinking water were provided ad libitum.

Experimental Design

The 12 guinea pigs were anesthetized by intramuscular injection of 5% tiletamin/zolazepam. The dorsal skin was shaved over an area of 7 × 15 cm and prepared with povidone–iodine. Barbed thread was implanted in the panniculus carnosus through an insertion point punctured with an 18-gauge straight needle. Four thread fragments of about 60 to 70 mm in length were symmetrically implanted into each guinea pig (Figure 1). Tissue samples from surrounding subcutaneous tissue, along with the thread, were harvested for histologic and molecular analysis at 1, 3, and 7 months after implantation. All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals provided by the Animal Laboratory Ethics Committee of the Department of Laboratory Animal Medicine, Medical Research Center, Yonsei University College of Medicine.

Histologic and Molecular Analysis

Tissue specimens were fixed in 10% formalin and embedded in paraffin. Transverse sections along the thread axis were stained with hematoxylin and eosin and Masson trichrome for analysis of the collagen.

In addition to histologic analysis, 3 biopsy specimens were obtained from each animal and embedded in

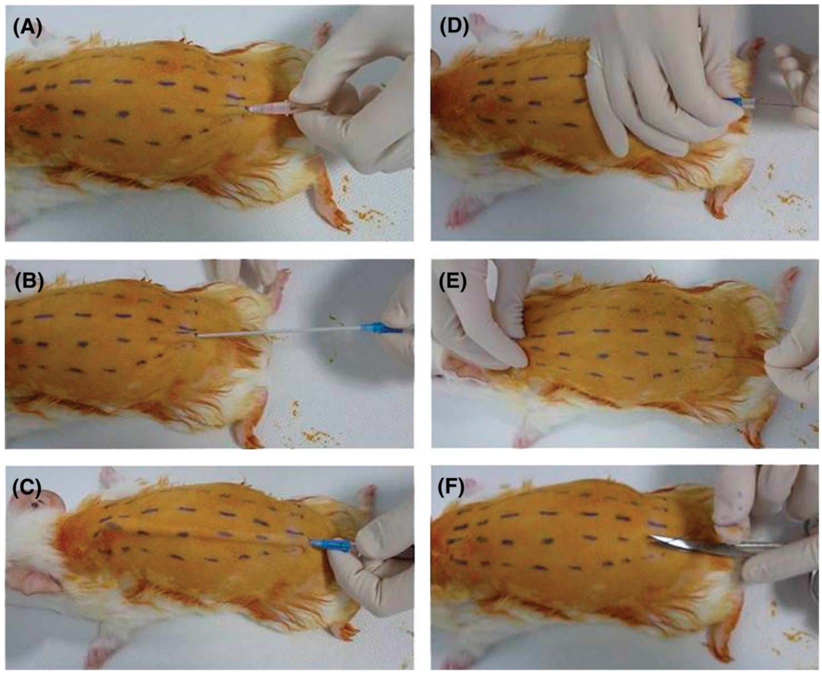

Figure 1. Threading under guinea pig dorsal skin. Barbed threads were implanted in the panniculus carnosus through an insertion point punctured with 18-gauge straight needle (A). A cannula, composed of a guide wire and a tube, was inserted in the direction of planned thread insertion. The guide wire was removed when the cannula reached the hypodermis along the panniculus carnosus (B and C). The thread was placed at the entry point of the cannula and advanced in a backward–forward motion (D). The advancing end was fixed along the panniculus carnosus and the tube was removed. Overlying skin is gently pushed upward. Each guinea pig was implanted with 4 fragments of 60 to 70 mm in length (E and F).

optimal cutting temperature embedding medium (Tissue-Tek OCT Compound Miles, Naperville, IL), frozen in liquid nitrogen, and stored at −80°C until ready for processing. Total RNA was extracted from tissues using TRIzol reagent (Invirtogen Life Technologies, Carlsbad, CA), and 2 μg of total RNA were converted to complementary DNA (First-Strand cDNA Synthesis Kit; MBI Fermentas, Vilnius, Lithuania). Quantitative real-time reverse transcriptase polymerase chain reaction (PCR) was quantified by the ABI 7500 system (Applied Biosystems). Real-time PCR amplifications were performed using SYBR GreenER Supermix with Premixed ROX (Invitrogen Life Technologies, Seoul, Korea) and amplified using the following primers: β-actin, F: 5′-AGCCAGCAGATCGAGAACAT-3′; R: 5′-ACTCTCCGCTCTTCCAGTCA-3′; COL1A1, F: 5′-AACGTGGTCTGCCAGGTATCF-5′, R: 5′-ACTCTCCGCTCTTCCAGTCA-3′; COL1A2, F: 5′-AACGTGGTCTGCCAGGTATC-3′; R: 5′-AGGACTGCCCACATTACCAG-3′; transforming growth factor beta 1 (TGF-β1), F: 5′-TACCTCAGCAACCAGCTCCT-3′; R: 5′-GCGAAAGCCCTCTAATTCCT-3′. Amplification conditions were as follows: initiation at 50°C for 2 minutes, 95°C for 10 minutes, followed by cycling conditions of 95°C for 10 seconds and 60°C for 1 minute for 40 cycles. Following amplification, melting curve analysis was performed from 50°C to 105°C, reading every 0.5°C.

Results

To investigate histologic changes related with implantation of barbed thread, the authors compared sequential alterations in dorsal skin samples harvested at 1, 3, and 7 months after implantation.

Histologic evaluation revealed the presence of visible threads surrounded by a fibrous sheath in samples obtained at 1 and 3 months after implantation. The capsular structure was thicker at 1 month than at 3 months (Figure 2A,B). Prominent tissue reactions showed the aggregation of inflammatory cells and fibroblasts centrally toward the suture material. At 7 months, the synthetic threads were difficult to trace. Meanwhile, granulation tissue composed of fibroblasts and multinucleated giant cells was noted at the

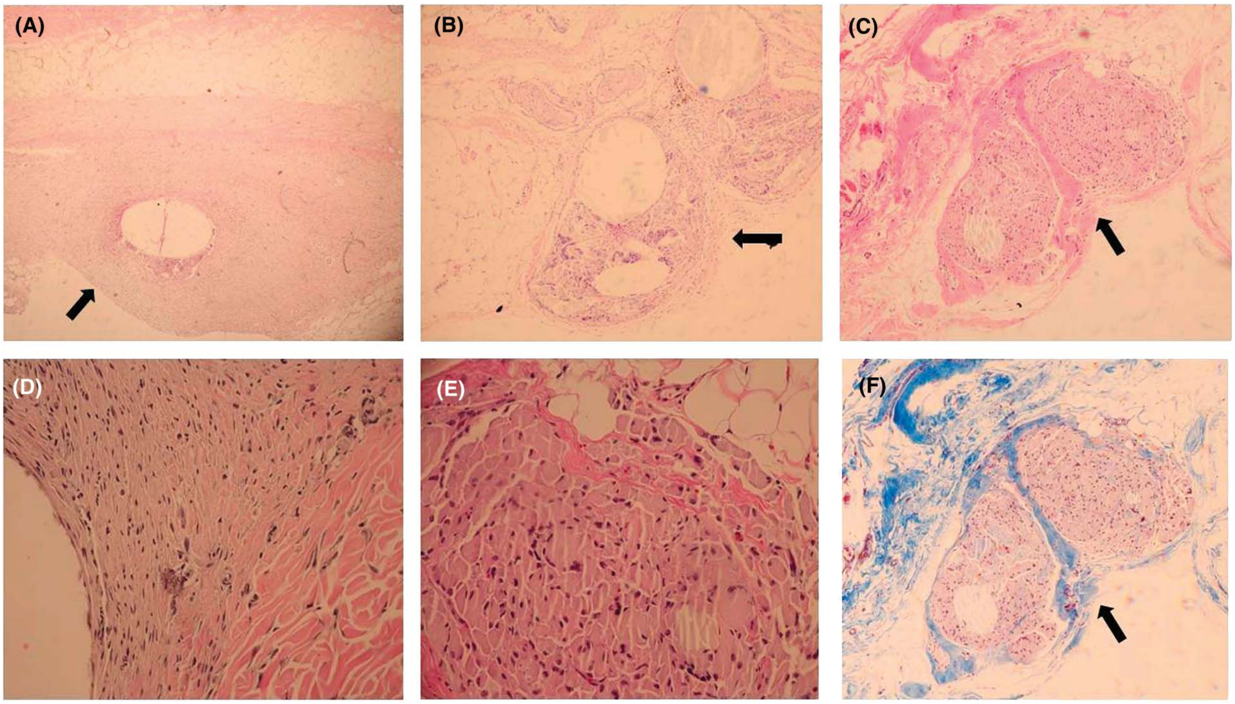

Figure 2. Histologic evaluation of capsule formation. Fibrous capsule (black arrow) around the inserted thread is well noted in a 1-month specimen (A). Fibrous sheath is still noted in a 3-month specimen (B). Inserted thread is degraded and the surrounding capsule is replaced by connective tissue (C and F) (A–C; hematoxylin and eosin ×40, F; Masson trichrome ×40). Strong tissue reaction with inflammatory cell aggregation is more prominent in a 1-month sample (D). Giant cell and granulomatous reaction are observed in a 7-month specimen (D and E; hematoxylin and eosin ×200).

insertion sites (Figure 2D,E). The overlying epidermis showed no prominent changes after implantation in all specimens. There were no abnormal injuries or signs of significant pathological phenomena noted on untreated portions of skin.

In Masson trichrome–stained sections, collagen fibers were stained blue. Dermal layers directly above the implanted thread showed denser collagen components compared to normal skin. The changes were more notable at 7 months than at 1 and 3 months. The fibrous sheaths surrounding the thread, which were noted at 1 and 3 months, were replaced with connective tissue at 7 months (Figure 2F).

Additionally, the authors quantified and compared collagen Type I and TGF-β_1 messenger RNA (mRNA) levels in tissue samples encompassing the site of thread implantation and normal skin at 1, 3, and 7 months after implantation. Assessment of molecular changes revealed statistically significant increases in collagen Type I (19.31 $\pm$ 7.13 times greater) and TGF-β_1 (6.12 $\pm$ 1.91 times greater) at 1 month ($p < .05$). At 3 months postimplantation, collagen Type I and TGF-β_1 expressions were, respectively, 7.70 $\pm$ 3.53 and 1.62 $\pm$ 0.31 times greater than that in normal skin. The increase was maintained until the end of the study at 7 months (collagen Type I [2.31 $\pm$ 1.17 times greater], TGF-β_1 [1.37 $\pm$ 0.26 times greater], $p < .05$) (Figure 3).

Discussion

In the present pilot study using guinea pigs, the authors investigated histologic and molecular changes for 7 months after the implantation of absorbable barbed thread. Our results revealed the development of a fibrous capsule along the synthetic thread, as seen in cadaveric skin and human subjects.[10,13] Other histologic findings were consistent with results reported in previous studies on animal models using either absorbable or nonabsorbable threads. Fibrous tissue and accompanying inflammatory cell aggregation were marked in early tissue samples up to 3 months. Prolonged implantation resulted in granulation tissue formation composed of giant cells that replaced the

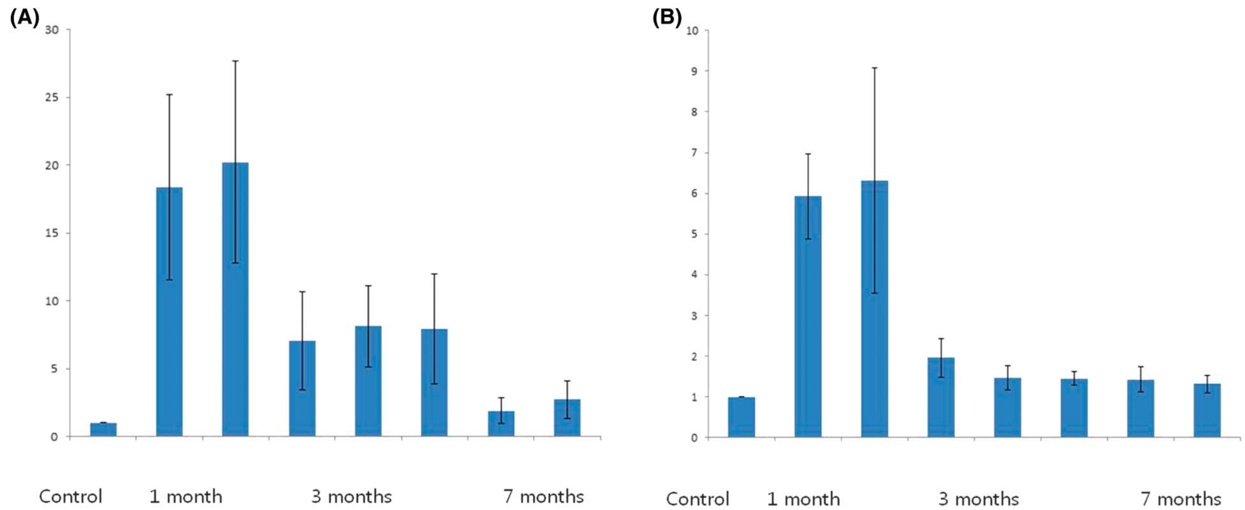

Figure 3. Changes in expression of collagen Type I (A) and TGF-β_1 (B) after thread lift, showing mean levels compared to nontreated section. Assessment of molecular changes indicated statistically significant increases in collagen Type I and TGF-β_1 at 1 month after implantation ($p < .05$). The increase was maintained until the end of the study at 7 months ($p < .05$). TGF-β_1, transforming growth factor beta 1.

fibrous sheath, along with a much reduced inflammatory reaction at 7 months postimplantation. Inflammatory reactions or disturbance of endothelial tissue on adjacent vascular structures, which may induce fibrosis or dermal remodeling, was minimal.

Early signs of aging in facial skin results from elastic tissue and collagen degradation, causing fine-to-deep wrinkles. In addition to decreased laxity, generalized thinning of subcutaneous fat tissue leads to volume depletion and a sagging appearance, especially on the mid-face.[2,17] With the advent of various cosmetic procedures for facial rejuvenation, minimally invasive modalities have gained in popularity.[18,19] Thread lifting evolved from the classic application of suspension sutures, which had been shown to cause substantial patient morbidity, mostly due to its complexity.[20,21] In preceding clinical reports, thread lifting was found to be effective in improving tissue laxity with shorter recovery time and less visible scarring.[7–9]

Various modifications to threads have been introduced, since Sulamanidze first introduced the concept of polypropylene barbed anchoring APTOS threads.[22,23] Suture material must be evaluated in both clinical and laboratory fields, assessing their longevity, complications, and side effects. Threads with larger diameters are expected to induce stronger biomechanical force; however, they are more liable to causing dimpling at insertion sites.[24–26] In this context, barbed threads carved with multiple cogs have been shown generate tensile strength equivalent to thicker nonbarbed threads. In previous animal studies, the greatest tensile strength and thickest capsule formation around the thread was measured at 1 month.[10,11]

In recent years, modified permanent or biodegradable suture systems have been introduced to thread lifting.[14] Nonabsorbable sutures show an initial tensile profile that is superior to absorbable material.[7] In the majority of cases, adverse events related to thread lifting are limited to early facial swelling or bruising that may resolve within a few weeks. Nevertheless, there are chances of thread being palpable or causing chronic inflammation in some patients due to implanted nonabsorbable sutures.[19,26]

Our study was undertaken to analyze chronological changes of absorbable lifting threads. The estimated biodegradation period of synthetic polydioxanone is 6 months. Thus, histologic evaluation alone is inadequate to determine the long-term effects of implantation beyond its absorption period. To investigate the possible dermal remodeling processes induced by thread lifting, the authors performed PCR to investigate molecular profiles. Our results showed that tissue surrounding the thread-inserted area continues to produce collagen after absorption. Quantitative levels of both Type I collagen and TGF-β_1 mRNA were significantly greater after absorption than at baseline ($p < .05$). As there were only minimal inflammatory reactions and no evidence of endothelial cell damage, which may affect dermal remodeling, the increase in dermal components can be assumed as a consequence of the thread lift.[10,11,13]

For optimal rejuvenation, especially for the midfacial area, restoring dermal extracellular matrix (ECM) proteins is important.[1,2] Studies of invasive and noninvasive modalities have demonstrated an increase in Type 1 collagen production with the expression of various signaling molecules.[27,28] Photothermal effects from laser or radiofrequency devices increased the TGF-β expression, which stimulates ECM remodeling by newly synthesized collagen deposition.[29,30] TGF-β signaling is traditionally well known to play a key role in wound healing processes, as it stimulates fibroblast proliferation.[31] Among its 3 isoforms (TGF-β_{1-3}), TGF-β_1 is more subjective to the analysis of collagen synthesis, as $\beta_{2,3}$ isoforms act via interaction with β_1.[32–34] Therefore, the authors aimed to strengthen the findings of present study by correlating TGF-β_1 expression with the levels of newly synthesized collagen. The authors postulate that the immediate lifting effect from mechanical anchorage is sequentially fortified with fibrous tissue formed along the thread resulting from initial inflammation. Afterward, a continuous biomechanical force of facial animation on the thread may trigger TGF-β signaling for dermal remodeling, which induces increase in collagen components. Our study represents the first investigation on the sustained effect of absorbable face-lifting threads and suggests that the clinical effect of absorbable sutures remains after complete absorption of the implanted thread.

The limitations of this study include a small number of samples and a lack of a control group. Also, there are inherent differences in the elastic and suture-holding properties of guinea pigs and living tissue, which may cause discrepancy from clinical technique. Further research with a control group and studies in live facial skin is required to further demonstrate its clinical effectiveness.

Conclusion

In this study, the authors evaluated the cutaneous changes induced by face-lifting thread in a guinea pig model. The results of the present study provide histologic evidence and quantitative molecular analysis that support the beneficial effects of thread lifting. Herein, synthetic absorbable thread-induced collagen synthesis lasted throughout the 7-month study period, and Type 1 collagen levels were correlated with increased levels of downstream TGF-β signaling. Therefore, the authors expect the rejuvenation effects of absorbable threads to be durable upon clinical application.

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