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SURGERY ARTICLES

Functional outcome of collagenase injections compared with fasciectomy in treatment of Dupuytren's contracture

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Abstract
Background This study was designed to provide comparative information on the safety and efficacy of injection with collagenase clostridium histolyticum (CCH) and fasciectomy for patients with Dupuytren's contracture (DC).
Methods A single-center, retrospective, observational, longitudinal chart review was conducted of 25 patients treated with CCH injections and 21 patients undergoing fasciectomy. Patients were assessed at 1 week, monthly for 3 months and then yearly for a minimum of 2 years after treatment for changes in contracture and range of motion, time to return to work/normal activities, patient satisfaction, and Disabilities of Arm, Shoulder and Hand (DASH) score.
Results Post-procedure follow-up averaged 32 months for the injection group compared with 39 months for fasciectomy group. For the CCH group, the mean postinjection contracture was 3.6° for the metacarpophalangeal and 17.5° for the proximal interphalangeal joints compared with 3.7° and 8.1° in the fasciectomy group, respectively. Patients treated with injections returned to normal activities after a mean of 1.9 days compared with 37.4 days for fasciectomy patients ($p<0.0001$). DASH scores for 13 CCH and 15 fasciectomy patients were obtained. The mean DASH score was significantly lower in the injection group in the first 3 months ($p<0.01$). At the 2-year follow-up visit, patients were satisfied with their outcomes following either treatment (92 % and 96 % of CCH and fasciectomy patients, respectively).
Conclusion CCH injections are safe and effective and may be a viable alternative to fasciectomy for treating DC. It also allows earlier return to work and daily activities.

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Introduction

Dupuytren's disease is a debilitating, potentially progressive disease characterized initially by the formation of palmar nodules. Over time, a collagen-containing, rope-like cord may develop, which can cause contraction of the metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints [16, 18]. Depending on the degree of contracture and the resulting deformity of the hand, patients' daily activities may become significantly affected, at which time they often seek treatment.

A variety of treatment options are available for Dupuytren's contracture (DC), ranging from nonoperative choices to surgical correction, which is generally reserved for more advanced disease with contractures of >30° for MP joints and >15° for PIP joints [6, 18]. Several different types of surgical procedures are used for treatment of DC cords, including fasciotomy; needle aponeurotomy; limited, regional/partial, or total/radical fasciectomy; and dermofasciectomy [16, 18]. The most commonly used surgical procedure is partial fasciectomy [18].

Patient risk factors and disease severity are important to incorporate into the surgical decision-making process [15, 23]. For example, fasciotomy is often recommended in the presence of a well-defined palmar cord, and more aggressive procedures such as dermofasciectomy are reserved for advanced or recurrent disease [16, 23]. Regardless of the surgical procedure used, overall surgical complication rates have been reported to range from 3.6 % to 39.1 % [6]. Potential complications observed may include nerve injury, pain, issues with wound healing, recurrence of disease, delayed return to normal activities, and the need for postoperative therapy [2, 6]. Additionally, there are limits to the number of surgical procedures possible on a single hand in a recurring disease such as DC. Nonsurgical and minimally invasive treatment options with demonstrated

comparable effectiveness may provide a less-invasive alternative to allow patients to recover functionality with minimal recovery time [19].

A minimally invasive treatment option, collagenase clostridium histolyticum (CCH; Xiaflex®[Auxilium Pharmaceuticals, Inc., Malvern, PA]/Xiapex®) has been approved in the US and Europe. CCH is indicated for treatment of adult patients with DC with a palpable cord [7, 21]. In published phase 3 studies, CCH demonstrated improved efficacy compared with placebo in reducing contractures and increasing range of motion (ROM). In these studies, safety was comparable between groups, and mostly transient, localized treatment-related adverse events were observed, which generally resolved without intervention [9, 11].

While multiple treatment options have been effective in patients with DC, there is no cure, and ultimately the disease may continue to recur and progress. Studies that examine the comparative effectiveness of different treatment options will be important when determining the role of each treatment during the course of disease and the impact on functionality and quality of life. Our retrospective, observational, longitudinal chart review of patients with DC treated with CCH injections or fasciectomy within the same time period was conducted with a follow-up period of at least 2 years. Clinical measurements (contracture, ROM), time to return to work, patient satisfaction, Disability of Arm, Shoulder and Hand (DASH) evaluation, and safety were compared to provide information on how each procedure may fit into current DC treatment regimens.

Materials and Methods

Data for patients with advanced DC who received CCH injections or who underwent fasciectomy in the same practice were reviewed retrospectively. Some of patients who received CCH injections were enrolled in the phase 3 Joint Open-label Injection Non-surgical Treatment (JOINT) study, where study drug was provided by Auxilium Pharmaceuticals (Malvern, PA) [20]. Patients were eligible to receive CCH injections if they had DC with a fixed-flexion deformity ≥20° and ≤100° measured by finger goniometry for MP joints and ≥20° and ≤80° for PIP joints in at least one finger other than the thumb caused by a palpable cord. Patients treated with CCH injections who were not part of the JOINT study were treated exactly according to the product label. No randomization was used in assigning patients to different treatment options. Patients were offered the two choices of treatment, and the patients who requested surgery rather than CCH injections were the ones who received surgical treatment.

Institutional review board approval was obtained. Informed consent was obtained from all patients and procedures followed were in accordance with the ethical standards of the Helsinki Declaration.

Measurements for flexion contracture (goniometer) and ROM were all assessed by the same hand therapists pretreatment and post-treatment. Patients were assessed at 1 week, monthly for 3 months, and yearly for a minimum of 2 years after treatment. Patients were evaluated for correction of deformity, active range of motion (AROM). Patients were asked regarding return to work and daily and sports activities and any limitations of doing those activities. Thirteen CCH injection and 15 fasciectomy patients completed a DASH evaluation form during each visit starting at 1 month postoperatively. Any complication was documented. Questions of patient satisfaction were measured according to a visual analogue scale (1–10) given at the 2-year follow-up visit, where scores of 8–10 indicated that patients were "fully satisfied" with treatment.

Recurrence of contracture in this study was defined as an increase of ≥20° from the point of correction as measured at the 2-year visit.

A total of 46 patients were treated during the study period, 25 patients and 32 joints with CCH injection and 21 patients and 29 fingers with fasciectomy. Of the 32 joints treated with CCH injections, 21 were MP joints and 11 were PIP joints. Of the 29 fingers treated with fasciectomy, 23 fingers had both affected MP and PIP joints and six fingers only had affected MP joints.

Treatment with CCH Injections

CCH was administered according to the protocol associated with the JOINT study, which is consistent with instructions given within the US prescribing information of the drug [17]. In brief, a 0.58 mg dose of CCH was injected (in 0.25 mL for MP joints and 0.20 mL for PIP joints) (Fig. 1), and approximately 24 h postinjection, a

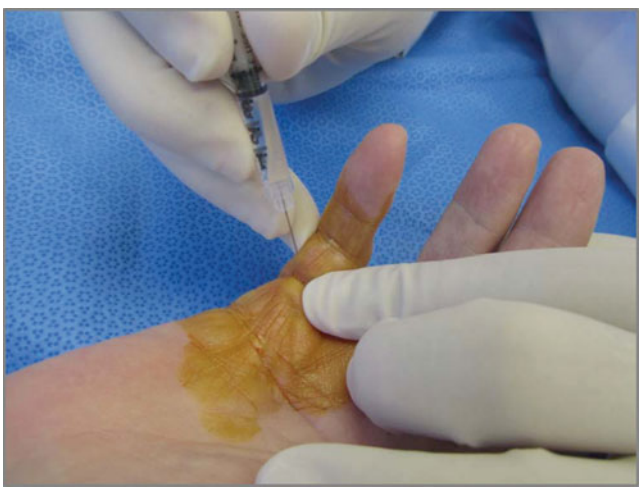

Fig. 1 Demonstration of CCH injections

finger-extension procedure was conducted to facilitate cord disruption [9, 11, 20]. The finger-extension procedure consisted of manipulation of the treated finger in an attempt to disrupt or distend the cord. It was recommended that the finger-extension procedure be performed no more than three times regardless of whether or not cord rupture occurred. Twelve patients received only one injection during the study period. Six patients received single injections in the MP joint of two different fingers, two patients received three injections in the same joint, two patients received two injections in the same joint, and three patients received two injections in separate joints (one MP, one PIP) with 30 days between injections per patient. Hand therapists were involved in fitting all patients with a night splint to be worn for 3 months following each injection and finger extension procedure.

Surgical Details of the Fasciectomy Procedure

An open fasciectomy with multiple Z-plasties was performed under axillary block anesthesia. In brief, a longitudinal incision was made along the volar aspect of the digit extending to the palm (Fig. 2). The digital neurovascular bundles were identified proximally, traced distally, and protected with vessel loops. The Dupuytren's cord was isolated and dissected from proximal to distal, while making sure that the neurovascular bundles and the digital flexor tendon sheath were protected. After complete excision of the contracted tissue, complete hemostasis was obtained. Multiple Z-plasties were performed at the level of the distal palmar crease, proximal digital crease, and PIP joint flexion crease. Nine patients had excision of the check-rein ligaments of the PIP joints since their PIP joint contractures were not corrected by the excision of the Dupuytren's cords.

The hand was splinted with full extension of the digit and slight extension of the wrist. Postoperatively, the splint was removed in 2–3 days, and the patient was started on AROM exercises. The patient continued to wear a night splint for 3 months following the surgery.

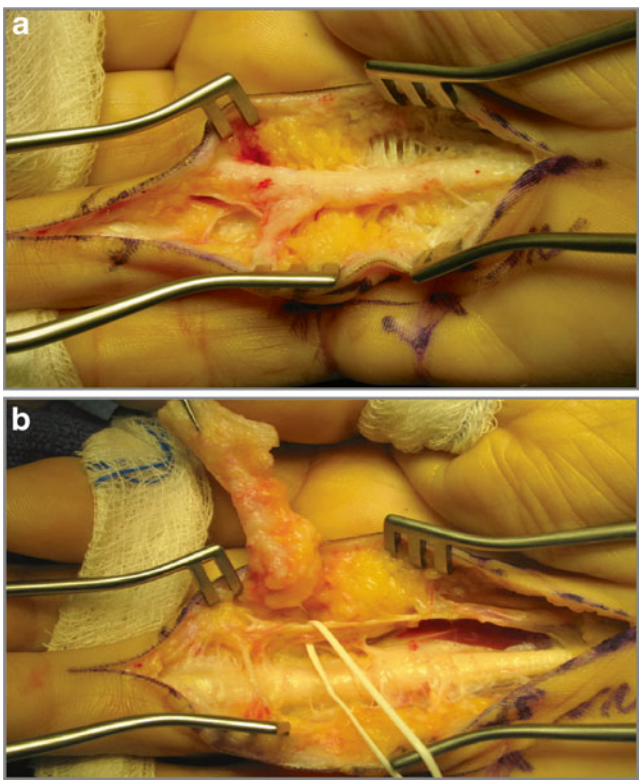

Fig. 2 Demonstration of the fasciectomy technique. **a** Isolation of the Dupuytren's cord. **b** Complete excision of the Dupuytren's cord

Statistical Analysis

Unless otherwise noted, continuous data are presented as the mean (±SD), and a pooled *t*test was used to determine the statistical significance of the group difference in means. A Fisher's exact test (two-sided) was used to compare the percentages of patients who were male between groups. The Wilcoxon rank sum test was used to compare the distribution of changes in contracture in patients treated with CCH for those joints with or without cord rupture, and for the return to work analysis.

Results

Patients collected for this retrospective study were mostly male (78 %) with a mean age of 66 years. Duration of DC symptoms ranged from 2 months to several years across both groups. More male patients received CCH injections (92 %) compared with those who underwent fasciectomy (62 %; $p=0.18$). Baseline contracture for patients treated with CCH injections and fasciectomy were comparable for MP and PIP joints (Table 1). Patients in the two groups were similar in term of work activities. Fifteen patients in the CCH group and 11 patients in the fasciectomy group were manual workers (Table 2).

Outcomes Following Treatment

The follow-up periods for patients treated with CCH injections or fasciectomy were 32 months and 39 months, respectively. For patients treated with CCH injections, the mean postinjection contracture was 3.6°±7.2° for the MP and 17.5°±10.6° for the PIP joints (Table 3). In patients treated with fasciectomy, the mean postoperative contracture was 3.7°±6.1° for MP joints and 8.1°±13.2° for PIP joints. Following treatment, mean change in contracture for patients treated with CCH injections or fasciectomy was–39.9°±21.9° and–37.7°±15.4°, respectively, for MP joints, and–12.5°±24.7°

Table 1 Baseline patient characteristics

Characteristic	CCH injection (n=25)	Fasciectomy (n=21)	p value[b]
Mean age, years (range)	65 (42–83)	67 (39–84)	0.69
Male, n (%)	23 (92)	13 (62)	0.18[c]
Treated joints per patient[a], n			
Total	32	52	–
MP	21	29	–
PIP	11	23	–
Little finger	9	9	–
Ring finger	8	11	–
Middle finger	3	8	–
Index finger	1	1	–
Contracture, degrees			
MP joints	43.5	41.4	0.76
PIP joints	30.0	29.9	0.99

CCH collagenase C. histolyticum, *MP* metacarpophalangeal, *PIP* proximal interphalangeal

[a] For CCH injections, the joint for injection was specifically indicated; for fasciectomy patients, joints were included if the baseline contracture was >0° and so would be independently considered for treatment

[b] Pooled *t* test was used to determine *p* values unless otherwise indicated

[c] Fisher's exact test (two-sided) was used to determine *p* values for gender

and −21.8°±15.3°, respectively, for PIP joints (Fig. 3). For MP joints, mean ROM post-treatment values were significantly different between treatment groups (p=0.02); however, the mean changes in both groups were nearly identical, with a mean ROM improvement of 40.7°±22.0° for patients treated with CCH injections and 40.6°±17.9° for patients treated with fasciectomy (Table 3).

When asked at follow-up visits, patients reported that they returned to their original work or normal daily activities (e.g., sports activities) an average of 1.9 days following CCH injections (range, 1–3 days) and 37.4 days following surgery (range, 27–61 days; p<0.0001). DASH scores were obtained and compared between 13 CCH injection patients and 15 fasciectomy patients. DASH is a self-administered quantitative test that consists of 30 base questions with eight added questions to assess work and sports activities. The total score is calculated on a scale of 0–100 with the higher scores denoting greater disability. The mean DASH scores of the 13 CCH patients was 3, 3, and 2 at 1 month, 2 months, and 3 months, respectively, compared with 38, 25, and 15 for the 15 fasciectomy patients, respectively. The difference in DASH scores between the two groups in the first 3 months was statically significant (Table 4). However, the difference at 1 year and 2 years was not statistically significant. Patient satisfaction was high with both treatments when measured at the 2-year follow-up visit, with 96 % of CCH injection and 92 % of fasciectomy patients reporting they were "fully satisfied" with their treatment.

Table 2 Work and sports activities of CCH injection and fasciectomy patients

	CCH injection (n=25)	Fasciectomy (n=21)
Construction workers	7	4
Manual laborers	8	7
Sedentary work (desk job)	3	2
Retired (golf or tennis playing)	2	2
Retired (no sports activities)	2	2
Homemakers (tennis playing)	2	1
Homemakers (no sports activities)	1	3

Of the 21 MP joints that were treated with CCH injections, 14 cords completely ruptured during the finger extension and seven did not. The mean postinjection contracture for the ruptured cords was 0°±0° and 7.1°±9.1° for those that did not rupture (p=0.03). The mean postinjection ROM was 50.6°±15.0° for those with cord rupture and 30.9°±24.5° for those without rupture (p=0.08). In the CCH treatment group, five PIP joints with baseline contractures of 10° were injected with CCH in the MP joint of the same finger; three of these five affected PIP joints had reduction in contractures to 0° when observed at the post-treatment follow-up.

Safety Considerations

For the patients who received CCH injections, the most common adverse event was bruising at the injection site (n=25). One patient had a transiently enlarged axillary lymph node, and one patient treated with fasciectomy experienced transient paresthesia of the radial side of the index finger, which resolved in 8 weeks.

No patients in this study met the criteria for recurrence (defined as an increase of ≥20° from the point of correction) as measured within the 2-year study period. However, a 15° increase was observed in one patient undergoing fasciectomy; 10° increases for patients treated with CCH (n=5) and fasciectomy (n=4) were also observed.

Discussion

From this study of two treatment options for patients with DC, most outcomes were comparable between CCH injections and fasciectomy, with the exception of time to return to work and resumption of normal hand function/use. Patients who received CCH injections returned to work or normal activities much more quickly than fasciectomy patients (2 versus 37 days). Patients in the injection group were able to use their hands in their regular work activities and normal

Table 3 Treatment outcomes by joint following CCH injections or fasciectomy

Characteristic	CCH injection (n=32)	Fasciectomy (n=29)	p value
MP	21	29	
PIP	11	23	
Mean post-treatment contracture (±SD), degrees			
MP	3.6 (7.2)	3.7 (6.1)	0.95
PIP	17.5 (10.6)	8.1 (13.2)	0.35
Mean decrease in contracture from baseline (±SD), degrees			
MP	−39.9 (21.9)	−37.7 (15.4)	0.73
PIP	−12.5 (24.7)	−21.8 (15.3)	0.45
Mean post-treatment ROM (±SD), degrees			
MP	90.7 (9.2)	83.3 (8.4)	0.02
PIP	67.5 (10.6)	88.8 (14.5)	0.06
Mean increase in ROM from baseline (±SD), degrees			
MP	40.7 (22.0)	40.6 (17.9)	0.99
PIP	15.0 (28.3)	27.8 (14.6)	0.29

CCH collagenase *C. histolyticum*, *MP* metacarpophalangeal, *PIP* proximal interphalangeal, *ROM* range of motion, *SD* standard deviation

daily activities much earlier than in the fasciectomy group as manifested by the statistically significant difference in the DASH scores between the two groups during the first 3 months. After 3 months, there was no significant difference in the DASH scores between the two groups. The shorter recovery time observed here following CCH injections could provide a considerable advantage for patients' quality of life.

The mean postinjection contracture following treatment with CCH was 3.6° for MP joints in this study, comparable to two published phase 3 studies of CCH reporting postinjection contractures of 7.2° and 7.5° [9, 11]. The mean postinjection contractures found for PIP joints in the phase 3 studies were 22° and 24°, which are higher than the 17.5° observed in this study. Also, in the phase 3 studies, injections with CCH resulted in mean reductions of contracture of 41° and 42° for MP joints and 33° and 32° for PIP joints [9, 11]. The mean reduction in contracture observed in the current study was 40° and 15° for MP and PIP joints, respectively. Additionally, in three patients with affected PIP joints who received CCH injections within the MP joint on the same finger, there was a decrease in contracture from 10° to 0°, which was most likely due to the fact that both joints were affected by a single cord.

Many studies have looked at the long-term results with fasciectomy [8, 14, 22]. A recent systematic review determined that the mean improvement in contracture ranged from 31°–51° for fasciectomy [5], and the 37.7° improvement in contracture for MP joints observed here falls within this range, although the observed mean change in contracture of 21.8° in the PIP joints was lower. Generally, PIP joints may not respond to treatment as well as MP joints, regardless of the method of treatment, as indicated by increased complications and difficulty in treating these joints [3, 4]. Most of the surgical patients in this study generally had more severe baseline disease (with both joints affected in many cases), which is demonstrated by the fact that, of the 16

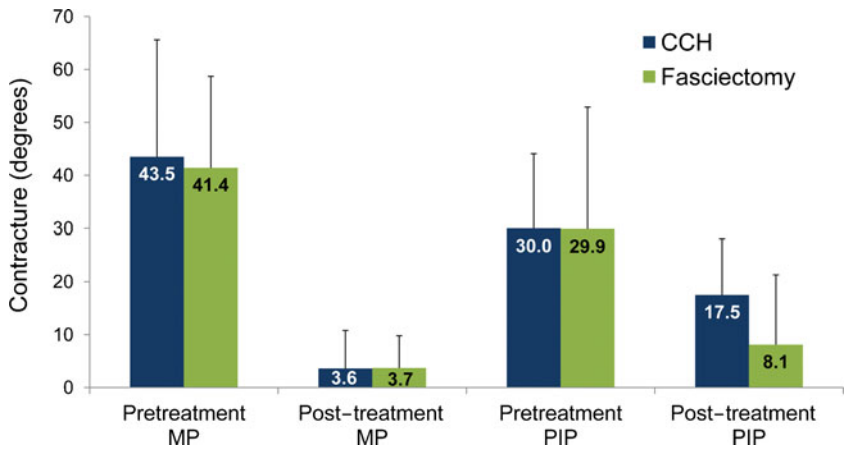

Fig. 3 Mean pretreatment and post-treatment contracture for fasciectomy and CCH injection by joint

Table 4 Mean DASH scores for the 13 CCH injection and the 15 fasciectomy patients

	CCH injection group	Fasciectomy group	*p* value
1 month[a]	3 (1–34)	38 (30–60)	0.002
2 months[a]	3 (0–30)	25 (15–45)	0.007
3 months[a]	2 (0–25)	15 (5–45)	0.02
1 year	2 (0–25)	4 (2–25)	0.5
2 years	3 (0–30)	3 (0–35)	0.6

[a] Denotes statistical significance

patients treated with fasciectomy, 21 MP joints and 17 PIP joints were affected. This may reflect a bias of patient selection in current practice as treatment with CCH injections was selected for patients with a single affected MP or PIP joint in most cases, while patients were considered for surgery regardless of how many joints were involved.

Because most of the patients who received CCH injections were treated according to the JOINT study protocol, anesthesia was not used during the finger-extension procedure. In ongoing practical experience, the use of anesthesia during the finger-extension procedure can result in more cord ruptures and less constrained manipulation, which may lead to additional contracture reduction. In this study, the postinjection degree of contracture was significantly improved in patients where the cord did rupture (0° versus 7.1°; $p=0.03$). The change in ROM was numerically improved in patients with ruptured cords, although this did not reach statistical significance. It should be noted that only a small group of unrandomized patients are being examined here, so statistical differences should be carefully considered.

Treatment with CCH injections, in this small study and in previously published studies, resulted in mostly local, transient adverse events that generally resolved without intervention [9, 11]. The complications observed in this study following fasciectomy were minimal; the published literature indicates that surgical complications, many of which occur rarely, may include injury to the tendon, nerve, or artery, loss of flexion or grip strength, complex regional pain syndrome, skin necrosis, wound-healing complications, or recurrence [1–3, 6]. There are also potential clinical challenges when performing reoperation following recurrence [6, 15]. A small number of cases have been reported where CCH retreatment has been used for DC recurrence without complication (unpublished data), but additional studies are needed.

While not directly measured in this study, the potential post-treatment costs associated with these two different treatment options may be considered by looking at return to work and the use of hand therapy following fasciectomy as surrogate measures. Hand therapists played a role in treatment of patients undergoing either procedure, as they collected all the measurements in this study. For patients treated with CCH injections, they were primarily responsible for fitting patients for their overnight splint. Patients who underwent fasciectomy were advised to see the hand therapist to develop an AROM program with scar massage and desensitization. Patients were instructed to perform these activities at home and were seen continually by the therapist in conjunction with their office visits. The fact that extensive hand therapy is not required following CCH injections may affect total cost of care and provide additional benefits, such as improved return-to-work times as observed in this study.

Generally, the postoperative hand rehabilitation protocol after surgery for DC is immobilization in a splint 24 h/day until wound healing is complete and then gradual decreased splint use over a 6-month period until limited to overnight use [10, 13]. When the wound has healed, ROM exercises and scar massage should be incorporated into the treatment plan three to four times daily [10, 13]. While incorporation of hand therapy and splinting is generally recommended following surgery in patients with DC, they have not always demonstrated improvements in outcomes [10, 12].

This study has an inherent weakness being a retrospective study. Also, the small sample size and the relatively short follow-up period may not allow adequate evaluation for potential recurrence. Nevertheless, our study demonstrates faster return to work and normal daily activities in patients treated with CCH injections compared with fasciectomy patients.

Overall, CCH injections appear to be as safe and effective as fasciectomy in this small group of patients. The shorter return-to-work time and the faster return to normal daily activities with CCH injections may be an advantage following treatment with CCH. Although this study only looked at a small number of patients from a single site, it suggests that CCH injections are a viable alternative to fasciectomy for treating DC. In order to determine the most appropriate treatment plan for patients with DC, comparative studies are needed to demonstrate the potential role of different treatment options and their place within current treatment paradigms.

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Statement of Human Rights The procedures described in this manuscript were in accordance with the ethical standards of the local and national responsible committees on human experimentation and with the Helsinki Declaration of 1975 as revised in 2000.

Statement of Informed Consent All patients included in this study were given detailed informed consent. All patients expressed their understanding of the details of the consents before signing then. Every patient signed the informed consent.

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