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Multicenter retrospective cohort study

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Franco Bassetto[1], Giorgio Pajardi[2], Bruno Battiston[3], Massimo Corain[4], Silvia Sargenti[5], Carlotta Scarpa[1], Chiara Novelli[2], Cesare Tiengo[1], Andrea Vitali[6], Federico Facchin[1/7], Maddalena Bertolini[3], Luciano Cara[8], Giancarlo Caruso[6]

[1] *Plastic and Reconstructive Surgery Unit, Department of Neurosciences, University of Padova, Padua, Italy*
[2] *Department of Clinical Sciences and Community Health, The University of Milan, Milan, Italy*
[3] *Department of Orthopedics and Traumatology, Orthopedic and Trauma Center, AOU Città della Salute e della Scienza, Turin, Italy*
[4] *Department of Hand Surgery and Microsurgery, University Hospital of Verona, Verona, Italy*
[5] *Complex organizational structure of functional rehabilitation, Palagi Hospital(I.O.T.), Azienda USL Toscana Centro, Florence, Italy*
[6] *Hand Surgery Unit, Palagi Hospital (I.O.T.), Azienda Usl Toscana Centro, Florence, Italy*
[7] *Plastic Surgery Unit, Azienda ULSS 8 Berica, San Bortolo Hospital, Vicenza, Italy*
[8] *Orthopedics and Reconstructive Microsurgery Unit, Cagliari, Italy*

Efficacy and safety of Dynavisc® gel in prevention of scar adhesions recurrence after flexor tendons tenolysis in zone 2: Multicenter retrospective cohort study

AIM: *Dynavisc® is a novel surgical product made of carboxymethylcellulose (CMC) and Polyethylene Oxide (PEO) designed to reduce post-surgical adhesions in tendons surgery. A multicenter retrospective cohort study was performed to investigate the clinical safety and efficacy of the Dynavisc® gel in reducing post-surgical adhesions after flexor tenolysis in zone 2.*
MATERIAL OF STUDY: *Thirty-one patients suffering from stiff finger after flexor tendon repairs in zone 2 treated with standard release with (18 Dynavisc®-treated group) or without (13 controls) anti-adhesion gel application into the flexor tendon sheath and around the site of the tenolysis, were collected in five different hand surgery units. Safety profile and functional outcomes (based on TAM test and the The Quick-DASH questionnaire) were examined from patients' charts and analyzed.*
RESULTS: *The application of Dynavisc® posed no safety concerns and it was not related to any additional complication. The Dynavisc®-treated group showed greater progressive improvement of TAM value in all visits with superior TAM value at T(90) and T(180) compared to the control group.*
DISCUSSION: *Tendon adhesions are the main cause of flexor tendon surgery failure. Multiple strategies (i.e. robust tendon repair, early rehabilitation and lubricant or barrier agents) have been proposed to minimize their formation. Among different products described in the literature Dynavisc® showed a significant role in limiting adhesions formation in a recent experimental study.*
CONCLUSIONS: *This clinical study confirm the safety of Dynavisc® gel application in hand surgery demonstrating its potential long-term benefits after flexor tendon tenolysis.*

KEY WORDS: Flexor Tendon Repair, Tendon Adhesions, Tenolysis

Introduction

Trauma, surgery, infection and inflammatory diseases involving tendon are frequently associated with tendon gliding impairment due to the formation of adhesions from the extrinsic healing process [1,2].
Due to anatomical configuration of the narrow digital canal containing superficial and deep flexor tendons, tendon injuries in zone 2 have always been a challenge for hand surgeons with significant risk of functional failure due to adhesions or rupture [3,4].
Once developed, adhesions are responsible for limitations in finger flexion and extension [5,6].
Accurate suturing technique and early rehabilitation fol-

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Correspondence to: Federico Facchin, Plastic and Reconstructive Surgery Unit, Departement of Neurosciences, University of Padova, Via Nicolò Giustiniani 2, Padua 35128, Italy (e-mail: federicofacchin@yahoo.it)

lowing flexor tendon repair provide the best chance of recovery [7,8].

The standard treatment includes tenolysis and early active assisted mobilization [9]. However the risk of adhesions recurrence after tenolysis is relevant, and physical therapy is often not enough to maintain immediate postoperative results [10].

In recent years, several lubricant pharmacologic agents including absorbable polymers, auto-cross-linked gel and hyaluronic acid based gel have been developed to improve post-operative results after tendon surgery [11,12]. The ideal product prevents fibroblast proliferation associated with extrinsic tendon healing without impairing the intrinsic tendon healing acting both as physical barriers or modulating the inflammatory process [13].

Dynavisc® gel is a compound of two polymers polyethylene oxide and carboxymethylcellulose that act simultaneously that has been shown to be safe and effective in preventing adhesion without interference with the healing process [14,15]. Carboxymethylcellulose prevents adhesions by acting as a physical barrier; Polyethylene Oxide is a high molecular weight polymer that prevents adhesions inhibiting the recruitment of fibroblasts [16]. A recent paper demonstrated the beneficial use of Dynavisc® gel in an experimental model of tendon injury [17]. The aim of the study was to evaluate the clinical impact of the gel in hand surgery.

Materials and Methods

A multicenter retrospective cohort study was performed under the coordination of the Italian Society of Hand Surgery (SICM) in five hand surgery units. All expert surgeons of different centers (GP, BB, MC, CT, GC) had similar levels of expertise in hand surgery, corresponding to level 4 and 5 according to Tang and Giddins [18].

All patients signed an informed consent in accordance with the Second Helsinki Declaration. The Ethical Committee of each center approved the study.

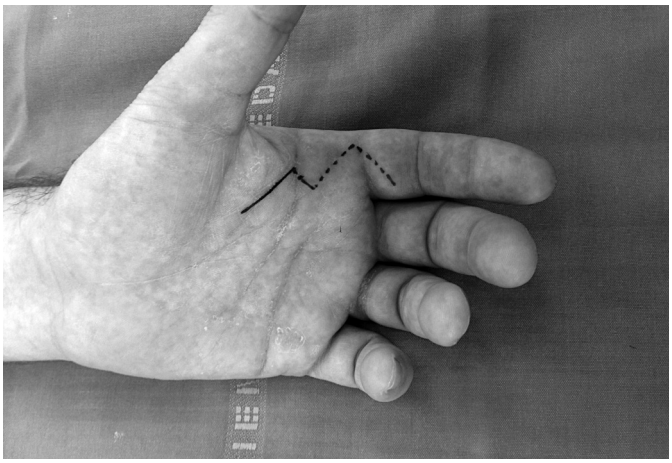


Fig. 1: Preoperative view: deficit in range of motion of the 2nd finger 100 days after both flexor tendons repair.

Patients

Thirty-one patients who underwent tenolysis for a stiff finger after flexor tendon repairs in zone 2 between 2012 and 2016 were collected according to the inclusion criteria described in (Table I), (Fig. 1). Their charts, functional and reported outcomes were retrospectively reviewed. Patients were divided into two groups based on whether or not the anti-adhesions barrier gel was used intraoperatively during tenolysis (Dynavisc® group vs. control group).

Surgical Procedure

The same surgical technique was performed for each patient according to a previous publication [12]. Under brachial plexus anesthesia and tourniquet control, access to the digital canal was made with a Brunner incision (Fig. 2). The same expert surgeon for each center performed the tenolysis with standard technique: A2 or A4 pulleys were preserved freeing the FDP tendon from the FDS tendon, from the tendon sheath and from the

Table I - *Inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria
– Adhesion after flexor tendon repair in zone 2 of a single digits (thumb excluded)	– Thumb adhesions
– Tenolysis performed at least 90 days from tendon suture	– Pregnancy, severe systemic comorbidities or affected by disease of musculoskeletal system *
– Male or female patients between 18 and 70 years of age	– Soft tissue involvement or loss preventing simple tendon repair
– Hand rehabilitation started maximum 48 hours after tenolysis	– Concurrent or previous fractures or post-operative interphalangeal joint osteoarthritis
– Written informed consent to be enrolled in the study	– Digital nerve involvement
	– History of previous lesion of the same finger

* *Unstable diabetes mellitus, autoimmune collagen diseases, cancer, blood clotting disease, psychiatric disturbances and smokers*

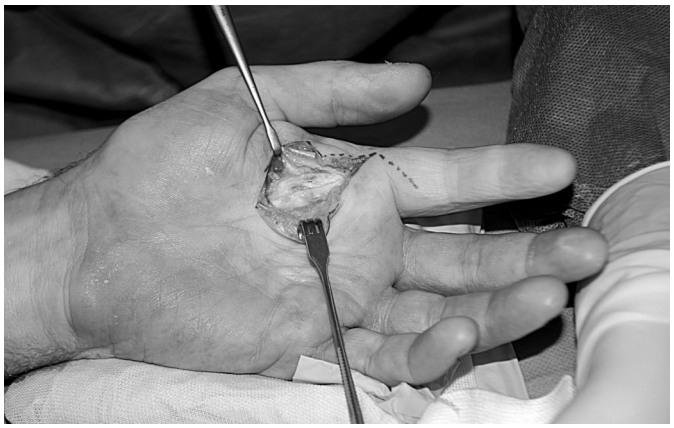


Fig. 2: Intraoperative view: adhesions release from the flexor tendons in zone 2.

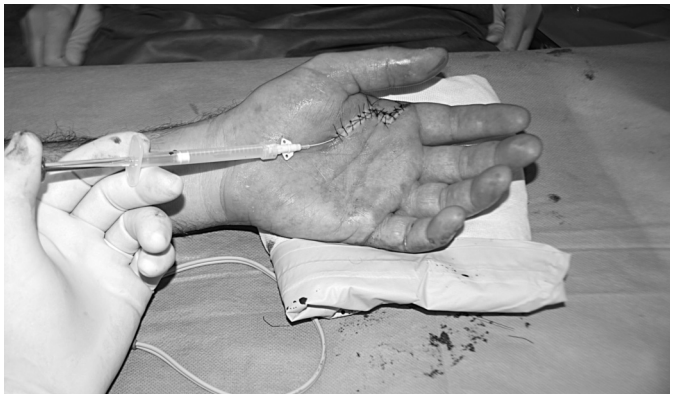
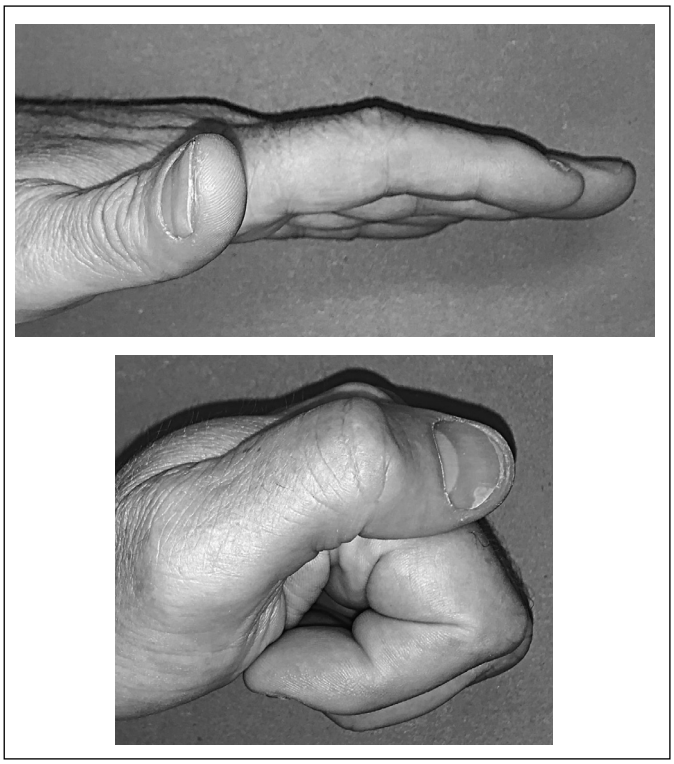


Fig. 3: Dynavisc® gel application



Figs. 4-5: Postoperative views: excellent recover of active ROM

scarred floor of the tendon canal [5,19]. At tourniquet release, hemostasis was achieved. After partial skin closure, Dynavisc® gel, supplied as 1 ml prefilled, sterile in single-use syringes, was injected along the exposed tendon surface and into the digital canal to fill the surgical area and beyond inside the digital canal. Final skin closure was achieved (Fig. 3). Postoperative pain was carefully controlled with per os painkillers.

Rehabilitation

A standard active-assisted rehabilitation protocol was started within the first 48 hours after surgery. Standard rehabilitation was divided into three stages. In the first week (days 2-7), the aim was to minimize edema and pain while maintaining tendon glide. Active exercises were performed according to the "place and hold" technique, described by Strickland starting 2 days after surgery [8]. In stage two (days 7-25), the aim was to move from prolonged and repetitive "place and hold" exercise to active assisted movements to ensure tendon and skin gliding. In stage three (day 26 onwards), the aim was to obtain the usual muscular force returning to full work activities at 12 weeks. The patient was asked to perform active flexion and extension exercise avoiding simultaneous extension of wrist and digits with subsequent resistive exercises and dorsal splint removal.

Evaluation

TAM values of each patient were collected at 30 (T30), 60 (T60), 90 (T90) and 180 (T180) days after tenolysis during rehabilitation protocol according to standard of practice (Figs. 4, 5). Total Active Motion was calculated according to Strickland and Glogovac as the sum of the degrees of active Proximal Interphalangeal and Distal Interphalangeal joint flexion less the degrees from full extension, while TAM% was calculated as TAM divided by 175° and the result is the percent score.
The Italian version of Quick-DASH questionnaire previously validated [20] as was administrated to each patient both pre operatively and after 180 days from tenolysis to compare pre and post operative patients' disability and symptoms. Patient compliance to the study (i.e. return to the visit, observance of assigned rehabilitation), concomitant therapies during the study period and any complications were recorded at each postoperative visit in a specific case report form.
Analysis of the efficacy was performed comparing TAM values of the two groups at each visit; changes in TAM value and TAM% pre and postoperative situation were calculated.

In addition, the assessment of TAM in categories excellent (>85%), good (70-85%), fair (50-70%) and poor (<50%) was performed in the two groups.

Statistical Methods

Data were entered into a Microsoft Access® database (Microsoft, Redmond, WA, USA) and analyzed using SAS System (SAS Institute, Cary, NC) by an independent contract research organization. Analysis of the efficacy was performed by the following variables: 1) TAM values observed at visits T30, T60, T90 and T180; 2) changes in TAM% in comparison with baseline; 3) assessment of TAM in categories: excellent (>85%), good (70-85%), fair (50-70%) and poor (<50%).
The differences in the four categories of TAM were analyzed using Fisher's Exact Test and Kruskal-Wallis test. The Kruskal-Wallis test, a non-parametric version of classical one-way ANOVA, compares the medians of the groups of data in x to determine if the samples come from the same population (or, equivalently, from different populations with the same distribution).
The Quick - DASH scores was analyzed with Student's t-test. All statistical analyses were conducted at a significance level of 0.05 and all tests were two-tailed.

Results

Thirty-one patients treated between January 2014 and July 2016 were included in the study analyzing surgical procedures, scheduled visits and follow up. 13 patients belonged to the control group and 18 to the Dynavisc® group (Table II). The recruitment performed in each center is reported in (Table III). The initial number of 20 patients to be compared retrospectively was reduced due to failure to follow up or to respect rehabilitative protocol. 60% of patients were males. The average age was comparable without statistical significant difference between the two groups. The most treated fingers in the Dynavisc® group were the 2nd and the 5th while the 5th finger was the least frequently treated in the control group. The days elapsed from the date of primary tendon surgery until the date of tenolysis (timing of tenolysis) was comparable in the two groups, more than 3 months and less than one year: 220 (SD 137) in the control group and 201 (SD 121) in the Dynavisc® group. All patients were followed up for 180 days after surgery through periodic visits.

Table II - *Summary of relevant demographic and clinical data*

		Control (n=13)	Dynavisc (n=18)
Mean age, Years (SD)		42.3 (10.3)	43 (11.3)
Gender	Male	10	8
	Female	3	10
Finger, n	2nd	4	7
	3rd	4	2
	4th	4	2
	5th	1	7
Timing of tenolysis, days (SD)		220 (137)	201 (121)

Table III - *Number of enrolled patients in each center*

Centre no.	Control	Dynavisc®	Total
1	9	6	15
2	3	3	6
3	1	3	4
4	0	3	3
5	0	3	3
Total	13	18	31

Efficacy Results

The mean preoperative TAM of symptomatic fingers before tenolysis was 119,9 (SD 47.7) and 112.3 (SD 46.9), while the mean preoperative TAM% was 46% and 42% in the control and Dynavisc® group respectively, without a significant difference as demonstrated by the t-test. After 30 days from surgery (T30) the TAM improved in almost all patients from the preoperative value except for two patients in the control group and two patients in the Dynavisc® group. The mean TAM values in each visit are reported in Table IV.
The Dynavisc® group showed a higher progressive improvement of the TAM values with time, compared to control group (delta) with a greater difference between groups at T(90) and T(180). No statistical significance was found with the Kruskal-Wallis test, however a trend towards a higher TAM value in Dynavisc group is confirmed (Fig. 6).
The assessment of digit function (excellent, good, fair, poor) at the last visit based on the TAM% value is shown in (Table V) and (Fig. 7). At baseline, all fingers in both groups had a fair or poor function, according to inclusion criteria. The main difference of function improvement between control and Dynavisc® groups was observed at T180.
Quick-DASH questionnaire scores were similar in the two groups at the preoperative visit and they did not show a significant difference in the study period. However, the Dynavisc® group showed a slightly greater improvement at T(180) (Table VI).

Safety Results

There were no recorded complications. No tendon ruptures, inflammation or adverse reaction were suffered by patients involved in the study.

TABLE IV - *Changes in TAM value in grades at follow up visits in comparison with basal/preoperative visit*

	Control (n=13) Mean (SD)	Delta of improvement after each visit	Dynavisc® (n=18) Mean (SD)	Delta of improvement after each visit
Pre	119.9 (47.7)		112.3 (46.9)	
T(30)	156.8 (33.6)	36.9	153 (29.8)	40.7
T(60)	171.8 (34.3)	15	171 (30.8)	18
T(90)	186 (26.8)	14.2	191.4 (30.7)	20.4
T(180)	194.8 (28.4)	8.8	209.2 (28.8)	17.8

TABLE V - *TAM% values before surgery and at T180*

	TAM pre%	TAM 180%	Difference
Control (n=13)	46 (18)	75 (11)	29
Dynavisc® (n=18)	42 (12)	81 (11)	39

TABLE VI - *Quick-DASH questionnaire results at T180 in comparison with basal visit*

Visit	Control (n=13) Mean (SD)	Dynavisc® (n=18) Mean (SD)	Total (n= 31) Mean (SD)
QD prePC	45.8 (12.6)	44.6 (16.3)	45.6 (12.6)
QD 180PC	22.7 (11.4)	21.0 (16.3)	21.2 (12.2)
Diff pre/post	23.1	25.6	

TABLE VII - *Anti-adhesions formation substances*

Substance	Efficacy	Surgery	Wound healing complications
Porcine gelatin and a polyglycan ester	N	Primary repair	Y
HA	Y	Primary repair	N
Topical 5-fluorouracil	Y	Primary repair	N
ACP® gel *	Y	Tenolysis zone II	N
CMC and PEO **	Y	Tenolysis zone II	N

**Auto-crosslinked polymer derived from hyaluronan; ** Carboxymethylcellulose (CMC) and Polyethylene Oxide (PEO)*

Discussion and Comments

Tendon adhesions and finger rigidity are among the most frequent and severe complications after surgery or injury repair in hand and fingers, with relevant impairment of patients' everyday life and workdays loss [6,21].

The elegant and fine tendon system can suffer from many types of insult and subsequent healing mechanisms are responsible for fibrin deposition and scar formation with functional impairment which is even more severe in case of associated fractures or nerve lesions requiring immobilization [22].

Zone 2 is particularly prone to adhesion formation due to the delicate relationship between superficial/deep flexor tendons sheet, Camper's chiasma, A2 pulleys and the complex extrinsic vascular supply. The high rate of tendon rupture and the need for tenolysis (24%) have been constant over the last 40 years [7,19,23-27]. Surgical strategies used to prevent surgical failure and minimize and balance adhesion formation and tendon ruptures include robust tendon repair (4 strands core and circumferential suturing as confirmed in vitro by Vlajcic et al [28]), possibly performed with Wide Awake Local Anesthesia No Tourniquet (WALANT) technique, alternative venting of A2 or A4 pulleys according to tendon suture impingement [3,29,30] and early active motion [8,31-37].

Nonetheless, 24% of flexor tendon repair in zone 2 require a tenolysis. Indeed, tenolysis is not free from complications, 16% of flexor tendon rupture after the procedure are reported in the literature [10].

Additional strategies have been proposed to reduce adhesions to limit the extrinsic healing process minimizing adhesions formation. Gel barrier, membranes and free gliding flaps have been described, however their availability in the clinical practice is limited [38-40].

Different materials evaluated in previous clinical studies are summarized in (Table VII).

Adcon T/N is a porcine-based gelatin used in spinal disc

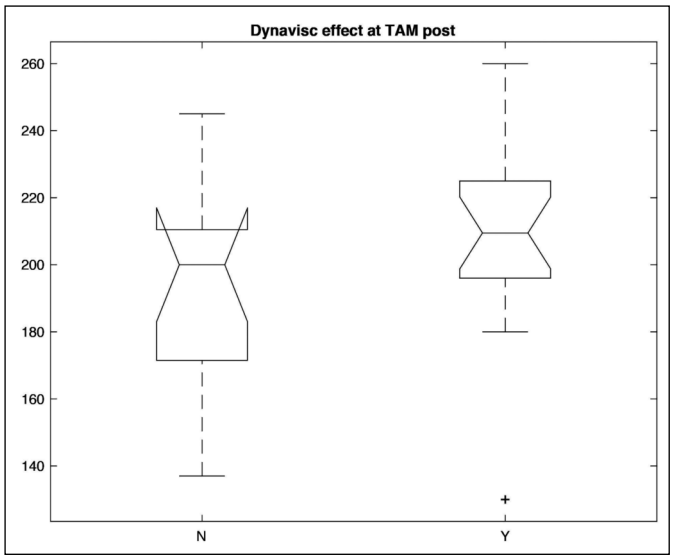


Fig. 6: The boxplot displays the TAM postoperative data. On the x-axis, use of Dynavisc® is depicted (Y stands for use of Dynavisc®, N stands for no use of Dynavisc®). The central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points, while outliers are plotted in red. Despite no significant results were found, the qualitative inspection of the data highlights a possible relationship between the use of Dynavisc® and higher TAM Post values. The qualitative result is enforced by the comparison between the two groups (p=0.0963, Kruskal-Wallis test).

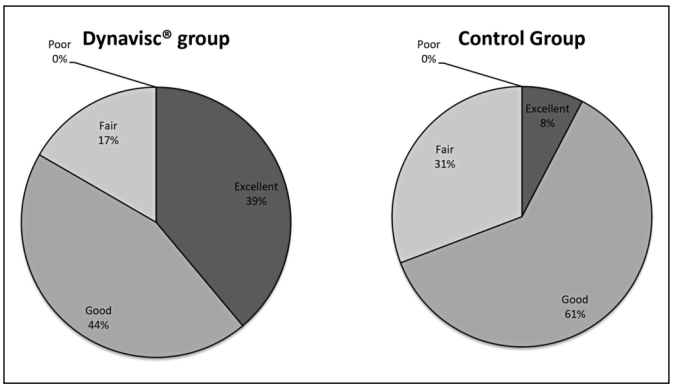


Fig. 7: Percentage of fingers with excellent, good, fair and poor function according to results of TAM%.

surgery which showed limited advantages in hand surgery, with potential wound healing delay observed in previous studies [7,41,42].

Topical 5-fluorouracil application showed improvement in immediate flexor tendon repair without healing complication [43,44].

Hyaluronic acid (HA) alone showed improved results without complications after 3 months when compared with placebo in a randomized controlled clinical trial [45]. However, experimental studies showed limited effect of HA due to rapid elimination and a limited effect on the healing process, bringing to a chemical modification of the molecule to prolong HA permanence over time [46,47]. An auto-cross-linked polymer of hyaluronic acid (HA) molecules showed to be advantageous in a clinical trial with a similar study design after tenolysis [12].

Previous clinical and experimental studies showed the efficacy and safety of barriers comprised of carboxymethylcellulose (CMC) and polyethylene oxide (PEO) in limiting adhesion formation [48-51].

A recent experimental study confirmed the role of Dynavisc® gel in limiting fibrous proliferation favoring the restoration of a functional digital canal in a model of acute flexor tendon injuries [17]. In addition, the long-term dissolution and the immunomodulatory effects over sensitive nociceptors supported by Polyethylene Oxide (PEO) component showed in previous study, could favor post-operative rehabilitative protocols [52].

This is the first clinical study evaluating the effect of Dynavisc® gel in flexor tendon surgery. The lack of complications, ruptures and stiffness recurrence demonstrated the safety of the gel in hand surgery. In addition, the functional results collected in this multicenter retrospective cohort study showed a potential benefit in the clinical use of Dynavisc® gel in tendon revision surgery. In fact, compared to the control group, Dynavisc® group showed higher functional improvement over time (Delta of improvement) suggesting a possible role in limiting the impact of adhesions in the long-term.

The authors agree with Boumediane et al. that the use of Dynavisc® gel is neither time-consuming nor invasive, even if it is related with additional cost for the procedure [53].

The retrospective design of the study, the limited numbers of participants, together with the heterogeneity of centers represent the main weaknesses of the study. However, it was necessary to adopt very restrictive selection criteria to recruit comparable patients in the two groups.

A multicenter clinical trial evaluating the efficacy of anti-adhesion devices should be performed to confirm preliminary results of the present study.

Conclusions

The study supports the clinical safety of intraoperative Dynavisc® application during tenolysis and it suggests possible long-term benefits of the anti-adhesion barrier favoring postoperative rehabilitation protocols.

Adequate primary repair techniques and correct primary rehabilitation protocols are the main instruments that aid hand surgeons to limit postoperative complication and adhesions in tendon surgery procedures.

Larger studies and clinical trials are needed to confirm the role of anti-adhesion substances efficacy in improving outcomes in primary and secondary flexor tendon surgery.

Acknowledgments

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CONFLICTS OF INTEREST: The authors declare that they have no competing interest.

Riassunto

OBIETTIVO: Dynavisc® è un nuovo farmaco composto da carbossimetilcellulosa e ossido di polietilene sviluppato per ridurre le adesioni post chirurgiche in chirurgia della mano. La Società Italiana di Chirurgia della Mano (SICM) ha coordinato uno studio di coorte retrospettivo per valutare la sicurezza clinica e l'efficacia di Dynavisc® nel ridurre le adesioni post chirurgiche a seguito di tenolisi flessoria in zona 2. Infatti, seppur utilizzabile nella pratica clinica, in letteratura non sono disponibili studi clinici su tale gel.

MATERIALE DELLO STUDIO: Trentuno pazienti affetti da rigidità digitale e deficit funzionale insorto a seguito di un riparo tendineo in zona 2 e trattati mediante tenolisi con (18 gruppo Dynavisc®) e senza (13 controlli) applicazione del gel anti-aderenziale Dynavisc® a livello della guaina flessoria ed a livello del sito di tenolisi, sono stati arruolati in cinque centri di chirurgia della mano italiani. La sicurezza del gel e i risultati funzionali (basati sul TAM test e sulla versione italiana validate del questionario Quick-DASH) sono stati raccolti dalle cartelle dei pazienti e analizzati.

RISULTATI: L'utilizzo del gel Dynavisc® non ha evidenziato problematiche di sicurezza né è stato associato ad alcuna complicanza. Il gruppo trattato con il gel ha mostrato un maggior miglioramento dei valori di TAM in tutte le visite con valori di TAM superiori rispetto al gruppo di controllo a 90 e a 180 giorni dall'intervento.

DISCUSSIONE: Le adesioni tendinee rappresentano la principale causa di fallimento della chirurgia tendinea. Molteplici strategie (riparo tendineo robusto, riabilitazione precoce e agenti lubricanti o barriera) sono stati proposti per minimizzarne la formazione. Tra i diversi prodotti descritti in letteratura, il gel Dynavisc® ha dimostrato un ruolo nel limitare la formazione di aderenze in un recente studio sperimentale.

CONCLUSIONI: Tale studio clinico conferma la sicurezza dell'uso del gel Dynavisc® in chirurgia della mano, evidenziando i suoi potenziali benefici a lungo termine a seguito di tenolisi dei tendini flessori.

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