RECURRENCE AFTER SURGERY FOR DUPUYTREN'S DISEASE: A RANDOMISED CONTROLLED TRIAL WITH DOUBLE BLINDING, COMBINING SEGMENTAL FASCIECTOMY WITH PLACEBO OR WITH NEO-ADJUVANT ORAL TAMOXIFEN

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Abstract

Prospective randomised double-blind study on the influence of tamoxifen (a synthetic non-steroidal anti-estrogen known to modulate the production of TGF beta and its influence on fibroblast function) on the healing process and the recurrence and/or extension of Dupuytren's disease after subtotal fasciectomy in high risk patients, graded 4 or more according to the scale of Abe, with a follow-up of 2 years after surgery (with unblinded extension to 5 years follow-up). The protocol was made up according to the CONSORT standards. The rationale is that tamoxifen has shown its efficiency on fibroblast activity in vitro and in vivo. Clinical research was the main purpose of this study. A significant improvement in outcome was found, with a relative improvement of goniometric correction as measured by the Tubiana index, of 93% with tamoxifen and 61% with placebo. Also, visual analogue scales for satisfaction showed an improvement in the tamoxifen group of 26%, compared to 6% in the placebo group. This study shows that neo-adjuvant use of tamoxifen can improve the surgical outcome of segmental fasciectomy in Dupuytren's disease in patients with a high diathesis.

The requirements put forward by the Declaration of Helsinki are respected. Study was approved by the Ethics Committee of the University Hospitals, KU Leuven IRB (OG032) nmbr ML 3936 on January 8th 2007.

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Introduction

Dupuytren's disease is a fibroproliferative disease causing important palmar contractures of the fingers. Various surgical techniques have been applied: collagenase injections, fasciotomy, segmental fasciectomy, total fasciectomy, skin transplants, flap surgery.[2,10] Today only surgery can effectively correct this disabling condition, but recurrence or expansion of the disease is a major unpredictable problem.[1,17] Indeed, recurrence rates, ranging from 39% to 71% have been mentioned.[14]

Several authors have tried to estimate the risk for recurrence and/or extension. A risk evaluation method has been suggested by Abe et al.[1] It is based on clinical signs, namely bilateral involvement, little finger surgery, early onset, plantar fibrosis, knuckle pads and radial side involvement; these variables were significantly correlated with recurrence. Rombouts *et al* found a correlation of recurrence (but not of extension) with the histologic stage, but only retrospectively.[17] Wilbrand *et al* found no relation of recurrence with activation markers of connective tissue, such as anticollagen type IV.[23] Citron and Nunez saw no correlation of recurrence with the type of incision.[7]

Active fibroblasts (myofibroblasts) have been shown to be a major component of the involved tissue in Dupuytren's disease. These cells are able to contract and probably contribute to the eventual finger contracture as seen in this condition. Different in vitro studies on myofibroblast cultures in collagen lattices have been run, to examine the influence of several agents on the contractile properties of these cells.[10,20,22] Transforming growth factors (TGF) beta1 and beta2 play an important role in the progressive fibrosis of Dupuytren's disease, and their downregulation may be useful in the treatment. In one study the effect of tamoxifen (a synthetic non-steroidal anti-estrogen known to modulate the production of TGF beta) on fibroblast function and TGF(beta2) downregulation in Dupuytren affected palmar fascia was clearly demonstrated on cultures in vitro: the contraction rate of collagen lattices, populated with fibroblasts obtained from Dupuytren affected fascia, and TGF(beta1) expression decreased under the influence of tamoxifen.[11]

Tamoxifen has been applied in vivo in aggressive fibrotic diseases, for example idiopathic retroperitoneal fibrosis and recurrent desmoid tumors.[5,8,9] Although the primary clinical application of this drug is breast cancer in female patients, it has also been used in males with breast cancer, gynaecomasty, prostate cancer and acromegaly, and proved to be well tolerated[9,15]. In these pathologies, treatment strategies include low-dose tamoxifen (30 mg orally per day), high-dose tamoxifen (60-120 mg orally per day).[4]

Based on this global information, we propose a prospective randomised double-blind study on the possible adjuvant effect of tamoxifen on subtotal fasciectomy in patients with Dupuytren's disease, who show a high risk for recurrence (Abe grade 4 or more).

Double blinding was provided to optimise the value of the suggested trial (the randomisation process, the physicians and patients as to therapy, and the physicians as to ongoing results).[3] The protocol was made up according to the CONSORT standards.[4,13,18]

Material and methods

This randomised controlled trial was set up as a mono-centre double-blind study at the Orthopaedic Department, University Hospitals KU Leuven. Patients were randomly allocated (1:1 ratio) to per oral tamoxifen 80mg/day or to placebo, during 12 weeks after surgery for Dupuytren's disease, if they carried a high risk for recurrence or extension, based on a D-score equal to or higher than 4. Thirty patients were randomised in a one-year period with a double-blinded follow-up for 2 years. This will be extended after unblinding to 5 years[21].
Primary outcomes were formulated in terms of absolute numbers in a Total Passive Extension Deficit (TPED)/ray, and relative numbers by the Tubiana index.
Secondary outcome was a Visual Analogue Satisfaction Scale (VAS). Also evaluated are scar tissue, sensitivity (two-point discrimination), recurrence and extension.
Dupuytren's diathesis, and thus risk for recurrence or extension after surgery, is evaluated according to the D-score (diathesis) formulated by Abe[1]: (a) bilateral hand involvement (with = 1, without = 0), (b) little finger surgery (with = 1, without = 0), (c) early onset before the age of 50years (1-0), (d) plantar fibrosis (2-0), (e) knuckle pads (2-0) and (f) radial side involvement (2-0).

D = a+b+c+d+e+f

If the D-score is higher than 4, there is a high risk of recurrence and extension: The study is carried out on a high risk group of 30 patients with a D-score higher than 4. They are randomised to either tamoxifen or placebo.

Participants

Inclusion criteria were Caucasian Dupuytren patients between 18-99 years old with risk score D of Abe[1] higher than 4, scheduled for subtotal fasciectomy, with a sample size of 30 patients (15/15) and a possibility for expansion if needed. They all agreed to avoid NSAID 6 weeks before until 12 weeks after surgery. Paracetamol was allowed. Also, smokers, diabetics, alcoholics and epileptics are allowed. Exclusion criteria were re-intervention, the need for skin grafts/flaps, premenopausal women, the use of NSAID 6 weeks before until 12 weeks after surgery, presence of (a history of) malignancy, known allergy to tamoxifen.
Reasons for withdrawal from the trial: simple request by the patient, even without giving a reason; decision by the investigator, based on suspicion of complications due to tamoxifen (side-effects, wound-healing problems); unexpected events such as serious illness; decision made by the Data Monitor.
Recruitment of the 30 high risk patients was done within one year in the out-patient clinic in the University Hospitals of the KU Leuven. Yearly about 100 Dupuytren patients are scheduled for surgery. Total follow-up is 2 years, eventually with extension to 5 years (but then unblinded).
In the trial entry procedure, participation was proposed by the investigators (Prof De Smet, Dr Degreef) to the eligible patients in the out-patient clinic. As soon as surgery has been decided, they received oral information, a "Patient information sheet" and an "Informed Consent" for home-study. This gave them time to think it over and to discuss it with their general

practitioner, who was informed by the investigator. The "Informed Consent" form and the "Clinical data sheet" (including TPED/ray; Tubiana index; clinical picture; VAS) were completed at entering into the trial 6 weeks before surgery on the preoperative anaesthesiologist outpatients evaluation , when the medication was started.
The population for analysis consists of all randomised patients being the Intention to Treat Population. The Full Analysis Set (FAS) is the Intention to Treat Population minus those who withdrew between randomisation and start of tamoxifen treatment. The Per Population consists of the Full Analysis Set, minus those who withdrew during or after tamoxifen treatment.

Intervention

Surgery (subtotal fasciectomy) is associated with the intake of placebo or oral adjuvant Tamoxifen, 80mg a day, every morning, starting 6 weeks before surgery for 18 weeks, during which time extension splinting is applied in a strict. Tamoxifen and placebo are provided by the hospitals' pharmacist. Both items look exactly alike.
A strict postoperative protocol for splinting and exercises was prepared. The first clinical follow-up was set at 10 days for wound inspection and bandage change, and a splint was adjusted that day. The splint was worn for 8 weeks and patients were well instructed by the surgeon. The first four weeks, the patient wears the splint day and night, but removed the splint during the day every two hours, during two hours, and he performs flexion and extension exercises as instructed (actively and passively) during this time. After 4 weeks, the patient continued to wear the splint only during the night, for another 4 weeks; he continued his exercises during the day. Further follow-up was planned at 4,8,12, 18 weeks, 6 months, 1 and 2 years postoperatively. Medication was discontinued at 12 weeks after surgery, and splinting 9 weeks after surgery (splinting for 8 weeks).

Objectives

The main purpose of the trial was to establish whether tamoxifen improves the outcome in Dupuytren patients with a high risk for recurrence or extension after segmental fasciectomy.

Outcomes

The 2 primary outcome parameters were (A) the Total Passive Extension Deficit (TPED) of the MCP and PIP joints of the worst affected ray was measured with a goniometer, by two independent orthopaedic surgeons. The study focused on individual rays, rather than on patients, especially for computation of the data. This TPED was measured before surgery (Clinical Data Sheet), and 4, 8, 12, 18 weeks, and 6 months, 1 and 2 years after surgery. Clinical pictures will be made preoperatively and at every follow-up evaluation (palmar view and ulnar view, as a back-up). Next, (B) the Tubiana index was calculated to evaluate the relative gain in motion. This allowed defining if tamoxifen was more efficient in, for instance, the less affected hands.
The secondary outcome was (C)Visual Analogue Satisfaction Score (VAS) graded from 1 to 10 points was made up by the patient at every visit.

Also noted at every check-up are the sensibility (two-point discrimination), wound healing, scar formation (redness, width, keloid formation, tenderness), complications.
Tissue samples were taken during the operation to confirm the diagnosis. Part of this material was frozen for eventual later examination (immunohistochemistry).
In view of the outcome measures for complications, no serious complications were expected. If serious wound healing problems occurred (serious delay of healing, dehiscence, infection) tamoxifen or placebo treatment could be stopped. Also if other serious side-effects of tamoxifen were suspected, medication (tamoxifen or placebo) was stopped. Possible side-effects are flushing, oedema, thrombocytopenia, nausea/vomiting, vaginal bleeding, and very rarely: dizziness, venous thrombosis and embolism, vaginal infection, tumour flare-up; extremely rare: headache, allergy, leucopenia, anemia, alopecia, erythema multiforme, liver steatosis, cholestasis, hepatitis, vision problems. If complications occur, even though in classical tamoxifen indications such as breast cancer the dosage is lowered, in this study tamoxifen was stopped completely.

Sample size

Based on power calculations, a total of 30 patients were simply randomised (equal numbers) into 2 groups of 15. Sample size estimation was based on requiring a mean difference of 20 degrees TPED/ray between the placebo group and the treated patients. The following assumptions were made to compute the sample size:

° common standard deviation (SD) of 15°

° two-sided significance level of 5%

With these assumptions, a sample size of 30 patients (15 per treatment arm) provided about 95% power to detect an overall difference of 20 degrees/ray

Randomization: sequence generation

As soon as the patient signed the Informed Consent Form and filled in the Clinical Data Form, he received from the investigator one of 30 boxes, numbered from 1 to 30, containing either placebo medication or tamoxifen, according to his rang order in the study. There were be 15 boxes with tamoxifen, each with 126 doses of 80mg, enough for 18 weeks or126 days, and 15 boxes with placebo, each with 126 doses of placebo.

Allocation concealment

The data monitor of the study numbered the boxes at random, beforehand. The investigators used the boxes in the given order, without any knowledge of the content: tamoxifen or placebo. Blocking and stratification was not done.

Implementation

The investigators enrolled the participants and assigned them blindly to the tamoxifen or to the placebo group. They noted the number of the box on the informed consent form and all other forms which concern a given patient.

Each of them kept in his office a sealed envelope containing 30 smaller sealed envelopes, each stating the real content of a given box. These envelopes were prepared by the Data Monitor. The investigators could open these envelopes only in case of emergency.
All patients were to take their medication in the morning, during 18 weeks, starting 6 weeks before the operation.

Blinding

Patients, surgeons-investigators and pathologists-investigators were blinded: double-blinding. The Data Monitor is the only person to know to which group every patient belonged.
The success of blinding was evaluated by asking each investigator to guess to which group every participant was allotted, at the end of the study. This was compared with the real situation.

Statistical methods

Statistical computation was based on all the randomised patients, according to the 'intention to treat' principle, including the patients who withdrew during the study. The patients who refused to take part in the study were mentioned.

I. PRIMARY OUTCOMES

A. TOTAL PASSIVE EXTENSION DEFICIT per RAY: TPED/RAY

Power calculations

30 patients are randomised (equal number) into 2 groups of 15. Sample size estimation is based on requiring a mean difference of 20 degrees per ray between the tamoxifen group and the placebo group. The following assumptions are made to compute the sample size:

° common SD of 15°

° two-sided significance level of 5%

With these assumptions, a sample size of 30 patients (15 per treatment arm) provides about 95% power to detect an overall difference of 20 degrees. A student's t-test is used.

B. TUBIANA INDEX

The Tubiana index is used to evaluate the relative gain in Total Passive Extension Deficit/ray will be used in order to find out if the tamoxifen treatment provided a significantly better result within each subgroup. A student's t-test is used.

II. SECONDARY OUTCOMES

C. VISUAL ANALOGUE SATISFACTION SCALE

A student's t-test is used to compare the results in both groups.

D. OTHER OUTCOMES

Will also be noted: sensibility (two-point discrimination), wound healing, scar formation (redness, width, keloid formation, tenderness), complications.

Results

PARTICIPANT FLOW

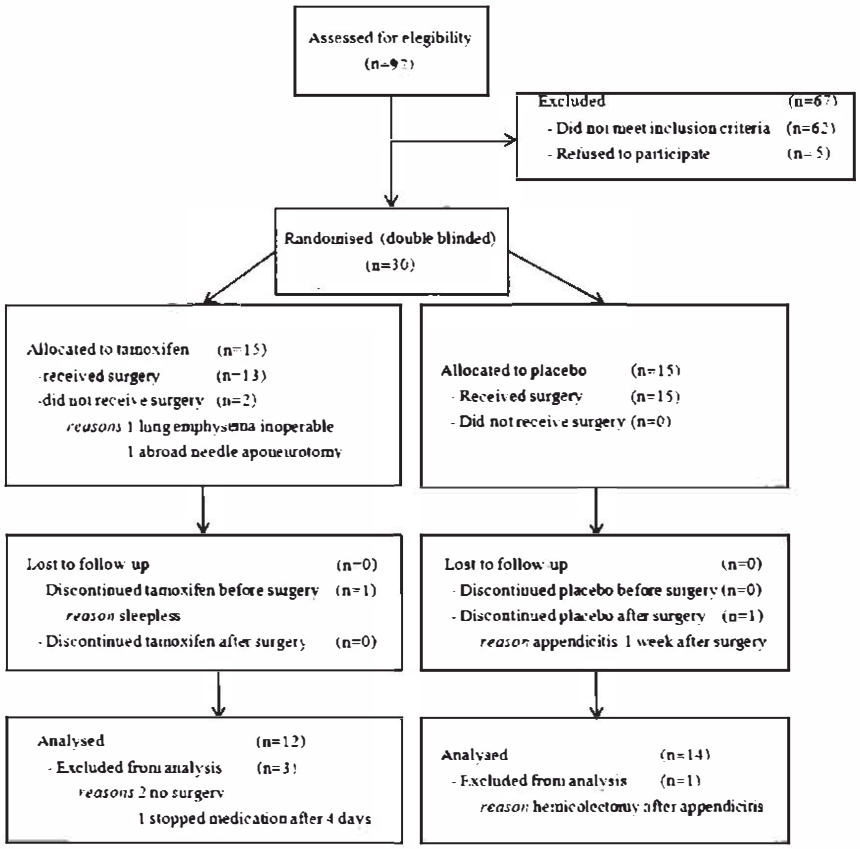

Figure 1 Flow diagram illustrating the participant flow from assessment of the eligibility, through the randomisation and towards the exact numbers that are analysed in the end.

RESULTS. RECRUITMENT

At this point, the period of recruitment is now 12 months. The period wherein the surgical interventions were performed is 14months, taking the 6 weeks preoperative medication start into account. Follow-up to this date is minimum 4 months to 1year. The clinical follow-up is continued in a double-blinded fashion.

BASELINE DATA

The included patients were allocated to a number. The inclusion was done in a randomized fashion. The intermediate evaluation were done in a blinded way, with the help of the study coordinator. Group 1 is the group with placebo and group 2 the tamoxifen. As illustrated in the following tables (table 1 and 2), the groups were very similar with a mean age of 64 and 62 years. In group 1, there were 4 female patients and 1 in group 2. All patients had a high risk score of Abe, higher than 4. The mean Abe score was 6 in both groups. Tables 3 and 4 illustrate the similar population in both groups, considering the goniometric extension lack. Group 2 had a (although not statistically significantly- slight different contracture, with a somewhat worse extension lack, mostly in the PIP joints.

Table 1 This table illustrates the population of group 1, the patients that had the placebo. Age, sex and presentation of the contractures are shown. The risk factors are noted and the score of Abe is calculated (Nr=number, M=male, F=female, Bil=bilateral disease, 50=onset under the age of 50 years, 5th= fifth ray surgery, LH=Ledderhose disease, KP=knuckle pads, 1st=1st ray involvement, Fam=occurrence of DD in the family). The line in light grey is not included in the final analysis, due to drop-outs as mentioned earlier in the flow diagram.

Group 1: placebo

Nr	Age	Sex	side	Right rays	Left rays	Abe	Bil	50	5th	LH	KP	1st	Fam
1	76	M	r	1,2,3,4,5	1,4	8	1	0	1	2	2	2	1
2	58	M	l	4,5	3,4,5	7	1	1	1	2	2	0	1
3	63	F	r	3,4,5	1,2,3,4,5	7	1	1	1	2	0	2	1
6	61	M	l	5	3,4,5	5	1	1	1	2	0	0	0
8	57	F	l	3,4	3,4,5	7	1	1	1	2	2	0	1
9	61	M	l	4,5	4	5	1	1	1	0	2	0	1
10	75	M	r	1,2,3,4,5	1,2,3,4,5	7	1	1	1	0	2	2	1
13	61	M	l	1,3,4,5	1,3,4,5	7	1	1	1	0	2	2	1
14	68	M	r	3,4,5	3,4,5	5	1	1	1	0	2	0	1
16	73	M	r	5	3,4,5	5	1	1	1	0	2	0	1
17	71	M	l	1,2,3,4,5	1,2,3,4,5	7	1	1	1	0	2	2	1
19	68	M	r	3,4,5	2,3	5	1	1	1	0	2	0	1
21	56	F	l	5	3,4,5	5	1	1	1	0	2	0	1
22	49	M	r	3,4	1,2	5	1	1	1	0	2	2	0
24	74	M	l	1,3,4,5	3,4,5	7	1	1	1	0	2	2	1
Mean (SD)	64(8.1)					6 (1.1)							

Table 2 This table illustrates the population of group 2, the patients that had the active tamoxifen. Age, sex and presentation of the contractures are shown. The risk factors and the score of Abe are noted (Nr=number, M=male, F=female, Bil=bilateral disease, 50=onset under the age of 50 years, 5th= fifth ray surgery, LH=Ledderhose disease, KP=knuckle pads, 1st=1st ray involvement, Fam=occurrence of DD in the family). Grey lines are not included in the final analysis, due to drop-outs as mentioned earlier in the flow diagram.

Group 2: active

Nr	Age	Sex	side	Right rays	Left rays	Abe	Bil	50	5th	LH	KP	1st	Fam
4	65	M	l	5	3,4,5	5	1	1	1	0	2	0	1
5	59	M	r	1,3,4,5	1,3,4	5	1	1	1	0	0	2	1
7	72	M	l	3,4,5	1,3,4,5	5	1	1	1	0	0	2	1
12	59	M	r	4,5	4,5	5	1	1	1	0	2	0	1
15	80	M	r	1,3,4,5	1,2,3,4,5	7	1	1	1	0	2	2	1
18	54	M	r	1,2,3,4,5	1,2,3,4,5	7	1	1	1	0	2	2	1
20	57	F	l	4,5	5	6	1	1	0	2	2	0	1
25	59	M	l	1,2,3,4,5	1,2,3,4,5	7	1	1	1	0	2	2	0
26	69	M	r	1,4,5	4	6	1	0	1	0	2	2	1
27	61	M	r	1,3,4,5	3,4,5	5	1	1	1	0	2	0	1
29	55	M	r	3,4,5	3,4,5	7	1	1	1	2	2	0	1
30	58	M	r	1,2,3,4,5	1,2,3,4,5	5	1	1	1	0	2	0	1
11	73	M		1,2,3,4,5	1,2,3,4,5	6	1	0	1	2	0	2	1
23	51	M		1,2,3,4,5	1,2,3,4,5	7	1	1	1	0	2	2	0
28	62	M		5	5	5	1	1	1	0	2	0	0
Mean (SD)	62(8.0)					6(0.9)							

Intraoperatively, a full extension of the fingers was achieved in all patients, except in 1 case: patient number 25 of group 2 with tamoxifen. His PIP contracture was not fully corrected during surgery, even after releasing the check rain ligaments. The intraoperatively achieved correction did however remain unchanged, even after 3 months.

NUMBERS ANALYZED

In group 1, there was 1 dropout (number 24). This patients had a severe complicated appendicitis in the week after the surgery, requiring a hemicolectomy. He therefore discontinued the medication. Although his postoperative evolution of the hand surgery was uneventful, with a full recovery, these data cannot be used for conclusions and were therefore not included for final analysis purposes.

In group 2, 3 patients were not included for final analysis. This was due to several reasons. Patient number 11 was known with severe lung emphysema, which had worsened 3 weeks after starting the tamoxifen, and he could not be operated on. He was lost for follow-up. Patient number 23 stopped the medication after 2 weeks, because he had sleepless night and he felt this was due to the stress of this medication and study. Although he was operated on and the results were good, no conclusions can be drawn and the data were not included for

final analysis. Patient number 28, although cooperative in the beginning of the study, decided after 3 weeks, that a needle aponeurotomy, which he had found on the internet (in Paris), was the new and better way, and therefore, he refused the segmental fasciectomy. Medication was stopped and there was no further follow-up.

OUTCOMES AND ESTIMATION

As illustrated in tables 3 and 4, the was a statistically different primary outcome between both groups. Group 2 had a (although not statistically significantly) slight different contracture, with a somewhat worse extension lack, isolated in the PIP joints. In group 1, there was a mean extension lack of 31° (0-62, SD 20.1) in the MCP and 47° (10-90, SD 30.0) in the PIP joints, making a total of 78° (29-135, SD 42.0) extension lack. In group 2, there was a mean extension lack of 30° (0-90, SD 31.8) in the MCP and 61° (26-96, SD 20.2) in the PIP joints, making a total of 92° (34-157, SD 42.3) extension lack.
There was a relative gain as calculated by the Tubiana index of 61% (39-100, SD 26.8) in group 1, compared to 93% (67-100, SD 13.2) in group 2. This is statistically significant as demonstrated by the student t test ($p = 0.001$). In the PIP joints, this was 49% (-50-100, SD 43.0) in group 1 and 89% (34-100, SD 21.7) in group 2, again, a statistically significant difference ($p = 0.007$).

Table 3 Group 1 with the placebo: goniometric results. (Nr = number ; ray = operated finger included in the measurements; pre = preoperative measurements; post = postoperative measurements; MCP =metacarpophalangeal joint; PIP = proximal interphalangeal joint, SD=standard deviation, grey lines were not included in the analysis no data where therefore shown)

Nr	Ray	pre mcp	pre pip	post mcp	post pip	gain mcp	gain pip	Gain% PIP	Total short pre	total short post	total gain	% gain
1	5	30	12	10	24	20	-12	-50	42	34	8	19
2	5	60	40	25	24	35	16	40	100	49	51	51
3	5	48	80	0	62	48	18	23	128	62	66	52
6	5	24	90	0	80	24	10	11	114	80	34	30
8	5	0	58	0	30	0	28	48	58	30	28	48
9	4	20	70	0	10	20	60	86	90	10	80	89
10	5	48	78	0	35	48	43	55	126	35	91	72
13	5	28	17	0	17	28	0	0	45	17	28	62
14	5	50	72	0	38	50	34	47	122	38	84	69
16	5	62	73	0	32	62	41	56	135	32	103	76
17	5	0	32	0	10	0	22	69	32	10	22	69
19	5	19	10	0	0	19	10	100	29	0	29	100
21	3	20	10	25	0	-5	10	100	30	25	5	17
22	4	20	20	0	0	20	20	100	40	0	40	100
	Mean	31	47	4	26	26	21	49	78	30	48	61
	SD	20,1	30,0	9,2	23,4	20,4	18,7	43,0	42,0	22,9	31,7	26,8

Table 4 Group 1 with the tamoxifen: goniometric results. (Nr = number ; ray = operated finger included in the measurements; pre = preoperative measurements; post = postoperative measurements; MCP =metacarpophalangeal joint; PIP = proximal interphalangeal joint, SD=standard deviation, grey lines were not included in the analysis no data where therefore shown)

Nr	Ray	pre mcp	pre pip	post mcp	post pip	gain mcp	gain pip	Gain% PIP	Total short pre	total short post	total gain	% gain
4	4	8	26	0	0	8	26	100	34	0	34	100
5	5	50	75	0	0	50	75	100	125	0	125	100
7	4	35	75	0	0	35	75	100	110	0	110	100
12	5	0	60	0	20	0	40	72	60	20	40	67
15	4	90	59	0	0	90	59	100	149	0	149	100
18	5	13	38	0	25	13	13	34	51	25	38	75
20	2	0	48	0	0	0	48	100	48	0	48	100
25	5	30	90	0	35	30	55	61	120	35	85	71
26	5	24	54	0	0	24	54	100	78	0	78	100
27	5	0	54	0	0	0	54	100	54	0	54	100
29	5	16	96	0	0	16	96	100	112	0	112	100
30	5	88	59	0	0	88	59	100	157	0	157	100
	Mean	30	61	0	7	30	55	89	92	7	86	93
	SD	31,8	20,2	0,0	12,5	31,8	22,1	21,7	42,3	12,5	44,1	13,2

As shown in figure 2, the comparison of the Tubiana index, reveals a significant difference in outcome improvement in group 2 with tamoxifen from 61% to 91%, even more pronounced in the most difficult PIP joints (from 49 to 89%).

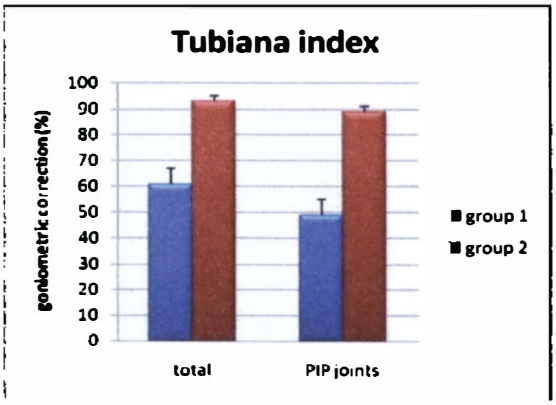

Figure 2 Comparison of the Tubiana relative correction coefficient in both groups. A significant difference (p = 0.001) is seen in total correction, where the placebo group showed a total correction of the MCP and PIP joints of 61% (SD 26.8) (group 1) compared to 93% (SD 13.2) in the tamoxifen group. Looking at the isolated PIP joint, which is most difficult to correct, the difference is also statistically significant (p=0.007) from 49% in group 1 towards 89% in group 2.

ANCILLARY ANALYSES

The secondary outcome measured with the VAS for satisfaction, also showed a significant difference between both groups (Table 5). Preoperative VAS score in group 1 was 7.6 (SD1.4) and did not improve significantly (p = 0.3) after the operation, toward the value of 8.2 (SD 2.0). Although preoperative visual analogue scores for satisfaction were somewhat worse (7.1, SD 2.1) in group2, they significantly (p = 0.0006) improved towards 9,7 (SD 0.9), demonstrating a high patients' satisfaction with the technique. There was a statistically significant difference in change in VAS for satisfaction between both groups (p = 0.02).

Table 5 Although preoperative visual analogue scores for satisfaction were somewhat worse in group2, they improved towards 9,7 (SD 1,2), demonstrating a high patients' satisfaction with the technique. (pre = before surgery; post = 3 months after surgery; vas = visual analogue scale range 1 - 10 points)

Group 1 Nr	VAS pre	VAS post	Change	Group 2 Nr	VAS pre	VAS post	Change
1	8	6	-2	4	9	10	1
2	10	10	0	5	8	10	2
3	7	8	1	7	6	10	4
6	8	4	-4	12	7	10	3
8	6	8	2	15	5	7	2
9	8	10	2	18	9	10	1
10	7	9	2	20	10	10	0
13	10	10	0	25	9	9	0
14	7	7	0	26	7	10	3
16	8	10	2	27	7	10	3
17	8	10	2	29	5	10	5
19	5	8	3	30	3	10	7
21	6	5	-1				
22	8	10	2				
Mean	7,6	8,2	0,6		7,1	9,7	2,6
SD	1,4	2,0			2,1	0,9	

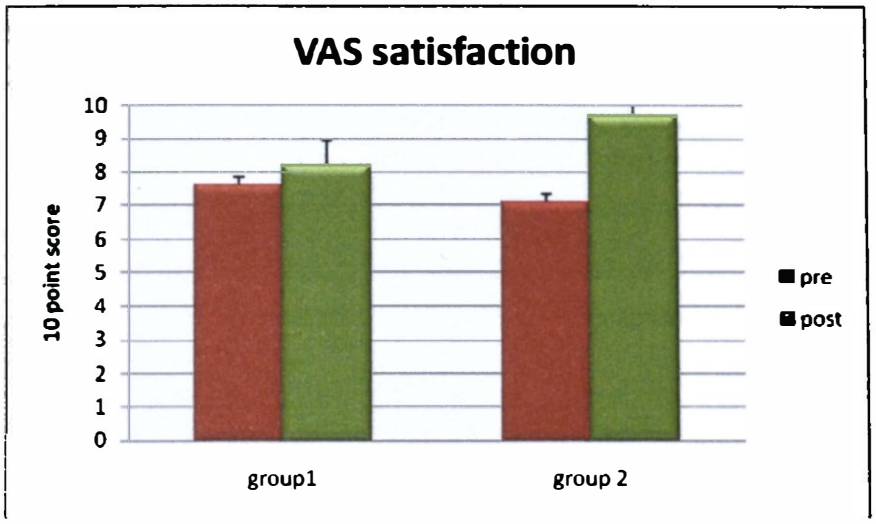

Figure 3 Illustration of the significant difference (p = 0.0006) in postoperatively improved visual analogue scale for satisfaction in the tamoxifen patients (group 2), but not in the pacebo group (p = 0.3) (group 1).

ADVERSE EVENTS

No serious complications were expected and non were seen. All possible side-effect, seemed to occur in the placebo group. In 3 cases a transient carpal tunnel syndrome was seen (2 male, 1 female) and although it was suspected that this might be enhanced by the use of the active component, which is an oestrogen and carpal tunnel syndrome is seen mostly in female patients, afterwards, all 3 patients appeared to belong to the placebo group. After 6 months, the female patients underwent a successful decompression of the carpal tunnel. Although 2 male patients complained of impotence, 1 transient and 1 continuing after 1 year, they both appeared to have taken the placebo. A male patient mentioned severe weight gain, again he belonged to group 1. A severe enteritis of a female patient with a hospital stay for 5 days 4 weeks after the operation, also occurred in group 1.

All wounds healed uneventfully, except 1 wound problem , with a slow wound healing process taking 3 weeks of granulating tissue. The patient had physiotherapy and although the extension of his finger was full, he could only flex completely in a passive way. A flexor adhesiolysis was therefore performed 3 months after the operation, and although successful, this did occur in a patient of group 2, taking the active tamoxifen.

In patient nr 12 of group 2, although the initial result was very good, we noticed a recurrence and some extension loss in the 3 months after the stop of tamoxifen. After this, the extension lack appeared to stabilize in the 1 year follow-up. This may point towards a rebound effect when stopping the medication abruptly.

Discussion

INTERPRETATION

The results in this study show a significant improvement in outcome of segmental fasciectomy in Dupuytren's disease in patients with a high risk for recurrence and high diathesis. Also, the satisfaction appears to be high and complications low with the neo-adjuvant use of highly dosed tamoxifen. No side-effects were noted and the study seems to stress the psychological aspect of impotence. The 1 wound problem that was seen, cannot lead to any conclusions, but monitoring of later use of this medication, does need to confirm the safety of highly dosed tamoxifen considering the wound healing process. The patient with a possible rebound effect, also drew some attention. Although this recurrent extension lack appeared to stabilize after 3 months, he did lose some of the correction. Although this only happened in 1 patient, future monitoring may reveal the real risk of this possible complication. In patients with severe forms of Dupuytren's disease, it may therefore be necessary to either continue the medication for longer periods (possibly in lower dosages), if not indefinitely as is often done in desmoids patients, or at least not to stop the medication to abruptly.

Naturally, the study needs more follow-up to evaluate long term outcome and therefore the monitoring will continue and a later report will be completed in term.

Strengths of the study are its double blinding, the CONSORT standards that were strictly followed, its strict randomization, the single surgeon and single technique and the similar populations with a high risk for bad outcomes, which increases the possible effect of the medication[13,16,18]. Weaknesses are the limited patient groups and the relatively high drop out in the active group. However, differences remained statistically significant and future studies are needed to confirm these findings and further assess potential risks.

GENERALIZABILITY

Although the use of tamoxifen may not be indicated in all patients with Dupuytren's disease, this study does bring enough evidence to certainly consider the use in patients with severe recurrent forms and a high family occurrence, in which case the patients may even share a possible negative personal experience of surgery, due to bad outcome and rapid recurrences. Here, the neo-adjuvant use of tamoxifen, possibly continued low dosage in the long term, may help in the fight against a disease which will never cure, but can only be put in a state of remission for as long as possible after a surgical correction of the hindering finger contractures. Since patients with Dupuytren's disease almost always present to the surgeon when contractures have already been established, the necessity for a surgical intervention will never disappear. However, with the new approach of identifying risk patients and considering the use of tamoxifen, disease recurrence and high-risk re-operations may be prevented in an important amount of patients in the future. This may avoid most amputations in revision surgery and severe recurrent disease. Patients with severe Dupuytren's disease, do need a life time-monitoring for timely intervention and if necessary, considering the (periodical) use of

tamoxifen if it flares (somewhat comparable with the treatment protocols in patients with rheumatoid arthritis).
On the other hand, the use of tamoxifen may also be considered in other wound healing problems as keloid formation in patients known with this problem or in families with systematic keloid formation. There are even families known with an associated keloid occurrence and Dupuytren's disease, which suggests a possible common pathway and/or genetic background.
There might even be a place for tamoxifen use in posttraumatic keloid formation as is known in burns.
Other pathological fibrotic processes as arthrofibrosis in shoulder surgery, which is possibly related diseases with Dupuytren's disease (as frozen shoulder occurs more frequent in Dupuytren's patients and on the other hand, patients with frozen shoulder syndrome often have Dupuytren's disease), may also benefit from tamoxifen use.[6,19] The use of tamoxifen may thus be considered for example in postfibrotic joint arthrolysis or even in a preventive way if a history of arthrofibrosis or severe Dupuytren's disease is present. Naturally, further studies and intense monitoring and reporting of the results will be needed to evaluate a possible effect and potential risks to this new approach.

OVERALL EVIDENCE

The use of tamoxifen is mostly known in breast cancer due to its oestrogen effect.[11] In this pathology, a long term experience with the drug has confirmed its safety as well as its efficacy in this pathology. Due to its fibroblast repressing effect, the use in desmoids tumours is also common.[9] However, due to the rarity of this tumour, no large series have been studied and some controversy about its effectiveness does exist. In retroperitoneal fibrosis, there are some studies confirming the possible positive effect on outcome.[5,8] In vitro studies of Dupuytren's myofibroblasts in the lab have confirmed a positive effect of tamoxifen on the cellular differentiation and contractibility.[11] Our study appears to confirm a positive effect on the outcome in Dupuytren's disease. This may be due to the suppression effect on the specific myofibroblasts in this disease. Also a generalized antifibrotic effect of the tamoxifen may have a positive effect on the result, since the wound healing process on itself is a fibroblastic proliferating and contracting event. This may also add to the wound healing problem seen in the I patient, and therefore careful monitoring in future use is obligatory.

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