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L E I R I A



DOENÇA DE PEYRONIE TRATAMENTO MÉDICO

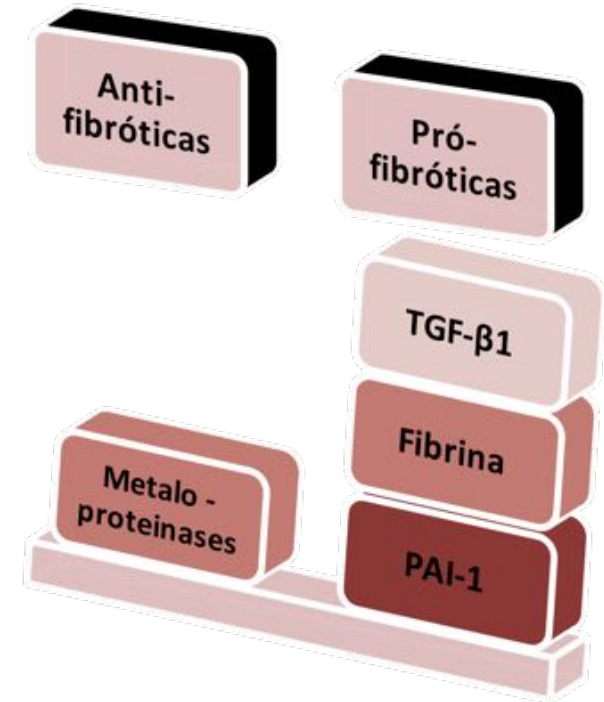
Leiria, 28 de Novembro de 2015.

Silvio Bollini.

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INTRODUÇÃO



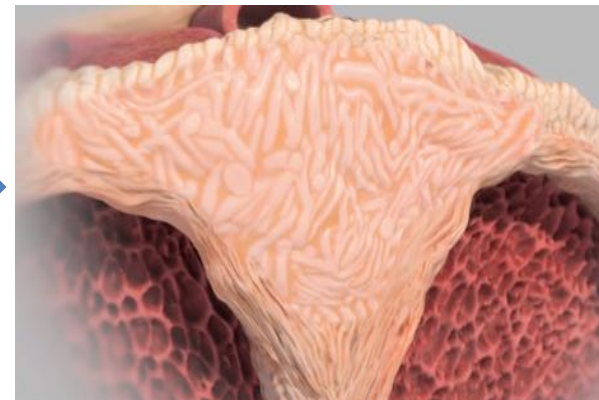
- **TGF-β1**: Inflamação, disrupção das fibras elásticas e deposição de fibrina.
- **Sobre-expressão TGF-β1** induz os fibroblastos a depositar mais colagénio – **placa fibrótica**.



HISTÓRIA NATURAL

FASE AGUDA

FASE CRÓNICA



48% ↑curvatura



40% estabiliza
40% dor

34% das placas fibróticas calcificam
Levine et al 2014

INTERVENÇÃO PRECOCE

Resolução espontânea é
rara (<10%)
Gelbard et al 1990



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Treatment of Peyronie's disease

Discuss natural history of the disease
Reassure patient that Peyronie's is a benign disease
Discuss current treatment modalities
Share decision making

Guidelines on Penile Curvature

L. Negro-Gonzalez, E. Potosky, J. C. Lopez, I. Serrano,
F. Garcia, S. Potosky, I. Serrano, A. Salas, T. Vera



HISTORY & PHYSICAL

BASIC ASSESSMENT

- Penile deformity
- Pain
- Palpable abnormalities
- Distress
- Interference with intercourse
- Establish active v. stable phase

PATIENT COUNSELING

- Typical course of PD
- Available treatment options based on phase
- Benefits/risks of treatment options
- Agree on realistic treatment goals

THERAPIES THAT SHOULD NOT BE OFFERED:

- Moderate Recommendations**
- Oral therapy with Vitamin E, tamoxifen, procarbazine, omega-3 fatty acids or vitamin E plus L-carnitine
 - Electromotive verapamil
 - Radiotherapy

PATIENT HAS STABLE DISEASE

Patient desires invasive treatment

PATIENT HAS ACTIVE DISEASE

Patient desires treatment of pain

EXPERT OPINION

Offer NSAIDs

CONDITIONAL RECOMMENDATION

- If inadequate pain control with oral medications, then may offer ESWT BUT:*
- Substantial patient burden
 - Rarely used in US
 - Does not reduce curvature or plaque

EXPERT OPINION

- Perform in-office intracavernosal injection (ICI) test with or without duplex ultrasound
- Document curvature, other deformities, presence/absence and degree of plaque(s) and ED

Follow and repeat assessment; if patient has reached stable disease state as indicated by absence of pain and non-progression of curvature, then may consider invasive treatments

MODERATE RECOMMENDATIONS

- Offer intralesional collagenase clostridium histolyticum with modeling by clinician and patient for curvature reduction (Grade B)
- Appropriate for patients with curvature >30 and <90 degrees
 - Patient must have intact erectile function with or without use of medications effects
- Offer intralesional interferon alpha 2b for curvature, plaque, and pain reduction (Grade C)

CONDITIONAL RECOMMENDATION

- Offer intralesional verapamil
Conditional Recommendation (Grade C)
- Note: evidence for efficacy is weak

Patient has stable disease and requires greater deformity correction than possible with intralesional treatments

Patient has intact erectile function with or without pharmacotherapy and/or vacuum device therapy

MODERATE RECOMMENDATION

- Offer tunical plication or plaque incision/resection with or without grafting (Grade C)

Patient does not have intact erectile function and/or has severe penile deformity and/or shortening

MODERATE RECOMMENDATION

- Offer penile prosthesis surgery with intraoperative adjunctive procedures, as necessary (Grade C)
- Use inflatable penile prosthesis (Expert Opinion)

Peyronie's Disease: AUA Guideline

Ajay Nehra, Ralph Alterowitz, Daniel J. Culkin, Martha M. Faraday, Lawrence S. Hakim, Joel J. Heidelbaugh, Mohit Khera, Erin Kirkby, Kevin T. McVary, Martin M. Miner, Christian J. Nelson, Hossein Sadeghi-Nejad, Allen D. Seftel, Alan W. Shindel and Arthur L. Burnett

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TRATAMENTO MÉDICO

- **Diagnóstico e referenciação precoce** – maior eficácia na fase inicial da doença.
- **Objectivos do tratamento:**
 - Estabilizar a inflamação e a placa peniana;
 - Diminuir a progressão da doença;
 - Diminuir a dor peniana
- Tratamento oral e minimamente invasivo: 1ª LINHA
- Até recentemente, nenhum destes tratamentos tinha aprovação.

Penile Curvature

E. Wessas, S. Hammar, S. Fakhour, S. Abd-Elrhman, I. Sardiya,
F. Shafiq, S. Fakhour, I. Wazir, A. Saleem, Y. Vardi

Oral treatments

Vitamin E

Potassium para-aminobenzoate (Potaba)

Tamoxifen

Colchicine

Acetyl esters of carnitine

Pentoxifylline

Intralesional treatments

Steroids

Verapamil

Clostridial collagenase

Interferon

Topical treatments

Verapamil

Iontophoresis

Extracorporeal shock wave lithotripsy (SWL)

Traction devices

Vacuum devices

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Oral Therapies

Colchicine

Pentoxifylline

Potassium aminobenzoate

Co-enzyme Q10

Topical Therapies

Magnesium or verapamil

Liposomal recombinant human
superoxide dismutase (LrhSOD)

Intralesional Therapies

Intralesional LrhSOD

Nifedipine

Parathyroid hormone

Dexamethasone

Betamethasone + hyaluronidase
+ lidocaine

Iloprost

Verapamil with or without
intralesional dexamethasone
and with or without lidocaine
electromotive

Electromotive Therapies

Electromotive verapamil + dexamethasone

Combination Therapies

Verapamil intralesional + oral L-carnitine

Verapamil intralesional + oral tamoxifen

Interferon intralesional + oral vitamin E

Verapamil intralesional + oral L-arginine
+ oral pentoxifyllineVerapamil intralesional + oral L-arginine
+ oral pentoxifylline + penile tractionOral vitamin E with or without (CI
treatments (papaverine, phentolamine,
PGE₁) and with or without oral colchicine
Ultrasound + hydrocortisone

Mechanical Therapies

Penile traction

Vacuum pump without the constriction ring

Hyperthermia



VITAMINA E (Tocoferol)

Mais prescrito na fase aguda

Dose 400 UI 1-2id; máx 3-6 meses (anticoagulante!)

Mecanismo:

Antioxidante (↓ radicais livres e NO – *indutores de fibrose*);

Reparação do DNA

Imunomodulação

Scardino & Scott
(1948) (n=23)

South Med J 41:173-177, 1948

- PLACA – SIM (91%)
- DOR – SIM (100%)
- CURVATURA- SIM (78%)

Associação Vit E + Colchicina – Muito utilizada.



POTABA (Para-aminobenzoato de potássio)

Dose 12g, durante 12 meses;

Mecanismo: efeito antifibrótico - ↑ captação de O₂ pelos tecidos;
↑ secreção de glicosaminoglicanos; ↑ actividade MAO;

Zarafonetis (1959) <small>J. Urol 81: 770-772, 1969</small>	<ul style="list-style-type: none">• PLACA – SIM• DOR – SIM• CURVATURA- SIM (85%)
Shah(1983*) (n=41)	<ul style="list-style-type: none">• PLACA – NÃO• DOR – SIM• CURVATURA- NÃO
Weider(2005*) (n=113)	<ul style="list-style-type: none">• PLACA – SIM• DOR – NÃO• CURVATURA- NÃO (estabilizou)

Ef. Adversos: náuseas, anorexia, prurido, ansiedade, sudorese, estado confusional –
abandono precoce da medicação!



TAMOXIFENO

Dose 20 mg 2id, 3 meses;

Mecanismo: modulação da secreção TGF β 1 pelos fibroblastos.

Ralph (1992)	<ul style="list-style-type: none">• PLACA – SIM• DOR – SIM• CURVATURA- SIM
Teloken (1999) (n=25)	<ul style="list-style-type: none">• PLACA – NÃO• DOR – NÃO• CURVATURA- NÃO

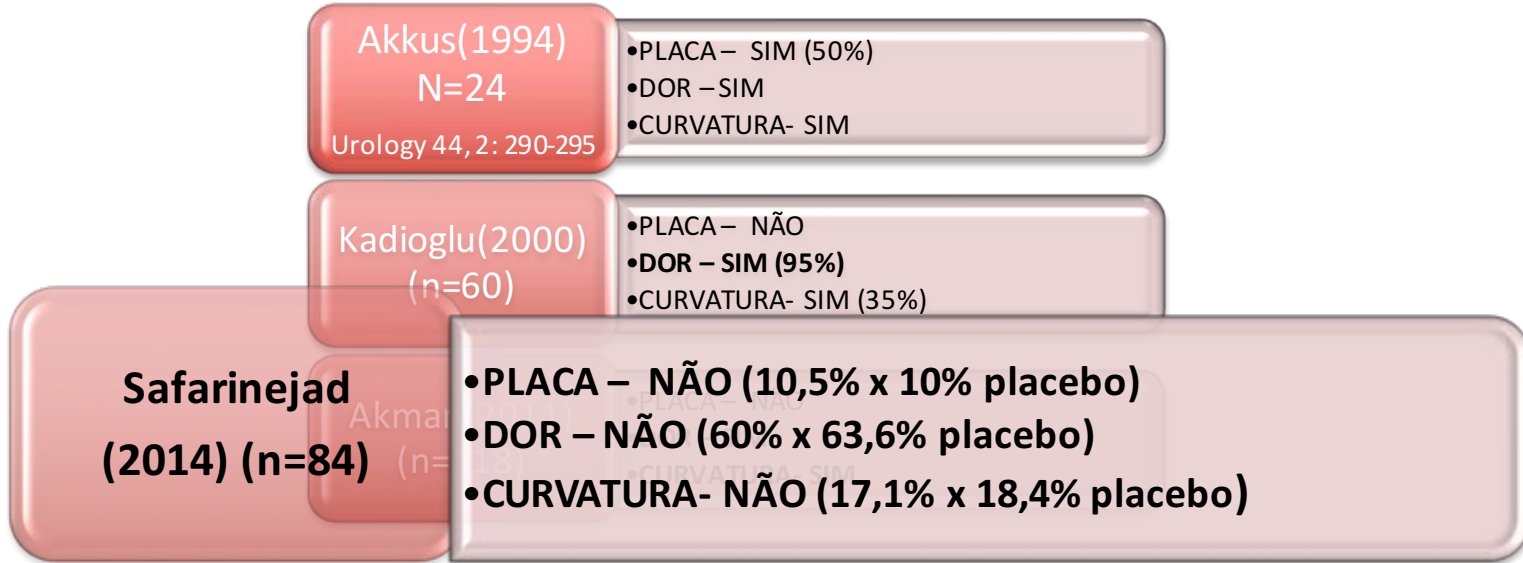
Ef. Adversos: hipercaliémia, edema periférico, depressão, tonturas, cefaleias



COLCHICINA

Dose 600-1200 mg id, 3-5 meses;

Mecanismo: efeito anti-inflamatório; ↓ ácido láctico



VIT E + colchicina (Prieto-2003): placa e curvatura (SIM); dor (NÃO)



CARNITINA

Dose 1g 2id, 3 meses.

Mecanismo: ↓ cálcio intracelular (?);

Supressão da proliferação de fibroblastos e da produção de colagénio

Biagiotti(2001) (n=48)	<ul style="list-style-type: none">• PLACA – NÃO• DOR – SIM• CURVATURA- SIM (estabilizada)
Safarinejad (2007) (n=59)	<ul style="list-style-type: none">• DOR – NÃO• CURVATURA- NÃO• PLACA - NÃO



PENTOXIFILINA

Dose 400 mg 3id, 6 meses;

Mecanismo:

Inibidor não-específico da fosfodiesterase;

↑NO prevenindo a progressão da DP ou revertendo a fibrose (fibrinolítico);

↓ cálcio na placa , ↓ depósito de fibrinogénio e altera a elastogénese por

↓TGFβ1

Smith(2011) (n=62)	<ul style="list-style-type: none">• PLACA – SIM• DOR – NÃO• CURVATURA- NÃO
Safarinejad (2010)* (n=114)	<ul style="list-style-type: none">• PLACA – SIM (p<0,001)• DOR – SIM• CURVATURA- SIM (p<0,001)



IPDE-5 (tadalafil)

Dose 2,5mg mg id, 6 meses;

Mecanismo:

Redução do colagénio; alteração relação colagénio III/I,
aumento do índice de apoptose na placa

Ferrini(2006)

BJU Int 2006 97(3): p. 625-33

- PLACA – SIM
- DOR – NÃO
- CURVATURA- NÃO



TERAPÊUTICA INTRA-LESIONAL

CORTICÓIDES

INTERFERÃO α -2b

Intralesional Injection of Interferon- α 2b Improves Penile Curvature in Men with Peyronie's Disease Independent of Plaque Location

Carrie A. Stewart, Faysal A. Yafi, Margaret Knoedler, Sree H. Mandava, Ian R. McCaslin, Prem Sant Sangkum, Suresh Sikka, Landon Trost and Wayne J. G. Hellstrom*,†

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Cipollone(1998)

(n=30)

- PLACA – SIM 40% (igual ao placebo)
- DOR – NÃO
- CURVATURA- NÃO

→ Não recomendado!



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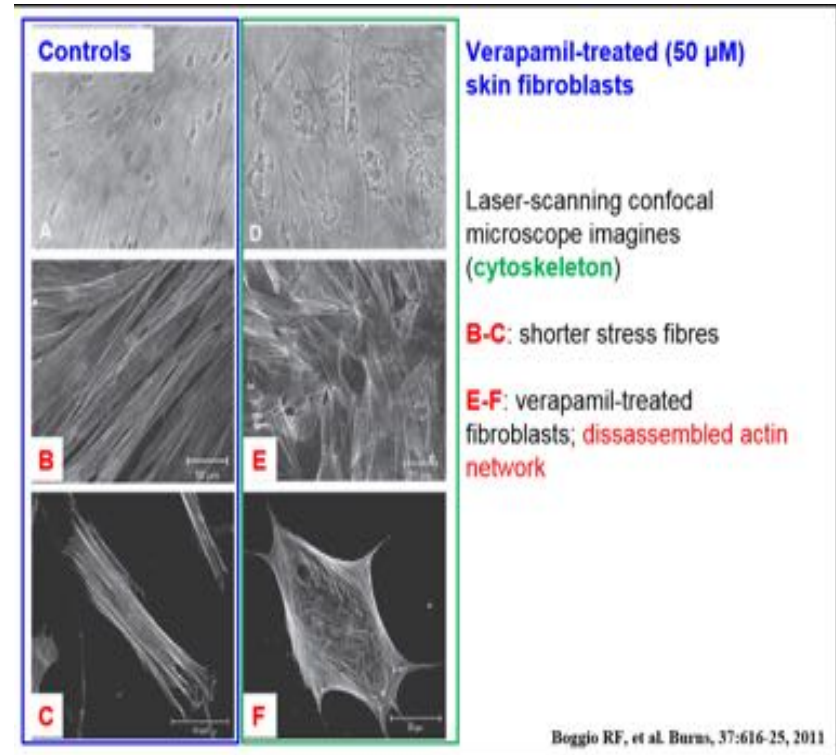
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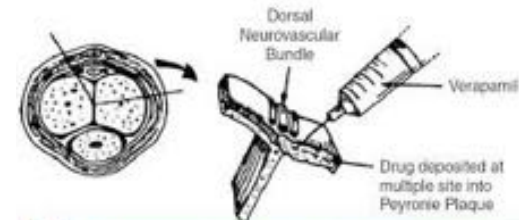
TERAPÊUTICA INTRA-LESIONAL

VERAPAMIL

- Dose 10 mg; 12 injeções/ 2 semanas;
- antagonista canais Ca; ↑ actividade da collagenase
- ↑citocinas inflamatórias e inibe a proliferação de fibroblastos *in vitro*



INTRALESIONAL INJECTION OF VERAPAMIL



Medscape

Source: Int J Injct Res. © 2008 Nature Publishing Group



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Estudos aleatórios, com grupo controlo de placebo

Treatment modality	Treatment Group N	Placebo Group N	Plaque size	Pain	Curvature
Oral					
Potaba (48)	51	52	<u>Reduction</u>	No effect	No effect
Vitamin E (51)	58	59	No effect	No effect	No effect
Tamoxifen (50)	13	12	No effect	No effect	No effect
Colchicine (49)	42	42	No effect	No effect	No effect
Carnitine (51)	59	59	No effect	No effect	No effect
Pentoxifylline (47)	114	114	<u>Reduction</u>	No effect	<u>Reduction</u>
Iontophoresis/EMDA (55)	23	19	NR	NR	No effect
Intralesional injection					
Verapamil (60)	7	7	<u>Reduction</u>	NR	Trend reduction
IFN α -2b (61)	55	62	<u>Reduction</u>	<u>Reduction</u>	<u>Reduction</u>
CCH (44,63)	111	36	NR	NR	Reduction
	22	27	NR	NR	Reduction
ESWT (53,54)	50	50	No effect	Reduction	No effect
	16	20	No effect	No effect	No effect
Penile traction*	NA	NA	NA	NA	NA

*Currently, no randomised, placebo-controlled studies examining penile traction are available.

CCH, collagenase clostridium histolyticum; EMDA, electromotive drug administration; ESWT, electro shockwave therapy; IFN, interferon; NA, placebo-controlled trial not available; NR, not reported; Potaba, potassium para-aminobenzoate.



TERAPÊUTICA INTRA-LESIONAL

Colagenase do *Clostridium histolyticum*

- Dose 10 000 U/0,25 cc – 2xs (24-72hs) – 4xs – 6 semanas
- Mecanismo: ataca selectivamente o colagénio (tipo II) da placa fibrótica.
- **Aprovado pela FDA para D.Dupuytren e D. Peyronie (2013)**
- Usado tanto em fase aguda/crónica.
- Dor peniana, contusões.
- Preço



Clinical Efficacy, Safety and Tolerability of Collagenase Clostridium Histolyticum for the Treatment of Peyronie Disease in 2 Large Double-Blind, Randomized, Placebo Controlled Phase 3 Studies

Martin Gelbard,^{*}† Irwin Goldstein,[‡] Wayne J. G. Hellstrom,[§] Chris G. McMahon,[‡] Ted Smith,[‡] James Tursi,[‡] Nigel Jones,[‡] Gregory J. Kaufman[‡] and Culley C. Carson III[‡]

- **PLACA – MELHORIA EM 34%**
- **DOR – SIM (93%)**
- **CURVATURA- SIM (36%)**
- **COITO POSSÍVEL – 75%**

Conclusions: IMPRESS I and II support the clinical efficacy and safety of collagenase C. histolyticum for the physical and psychological aspects of Peyronie disease.



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TERAPÊUTICA TÓPICA

ANDROLOGY



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ORIGINAL ARTICLE

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Keywords:

dexamethasone, intralésional injection, Peyronie's disease, transdermal electromotive administration, verapamil

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Comparison of transdermal electromotive administration of verapamil and dexamethasone versus intra-lesional injection for Peyronie's disease

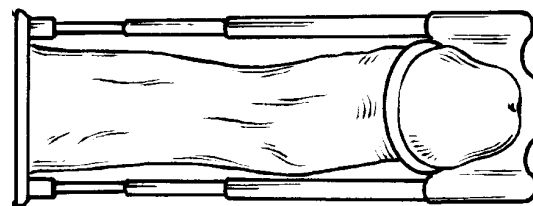
A. R. Mehraei,* F. Namdari,† A. Salavati,‡ S. Dehghani,§ F. Allameh¶ and G. Pourmand||

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- Remodelação placa.
- Reacção inflamatória.
- Activação Mos.

LEOC – tratamento semanal durante 4 semanas.

Peyronie's Disease Treatment The fsPhysioMed Extender



2-9 hs/dia – 6 meses



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Preferred term	Treatment-related AEs* (N = 1 044) n (%)
Penile haematoma (82.7% had the verbatum 'penile bruising')	524 (50.2)
Penile pain	350 (33.5)
Penile swelling	302 (28.9)
Injection site pain	252 (24.1)
Injection site haematoma	205 (19.6)
Penile haemorrhage (100% had the verbatum 'penile ecchymosis')	193 (18.5)
Penile oedema	139 (13.3)
Injection site swelling	135 (12.9)
Injection site haemorrhage	118 (11.3)
Contusion	74 (7.1)

Carson III et al. BJU Int 2015; 116: 815-822

Two CCH injections, with 24- to 72-hour period between injections, repeated after 6 weeks for up to four cycles improved penile curvature deformity and PD Symptom Bother

Gelbard M, et al - J Urol 2013;190:199-207.



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ORIGINAL ARTICLE

Combination of intralesional verapamil and oral antioxidants for Peyronie's disease: a prospective, randomised controlled study

V. Favilla¹, G. I. Russo¹, S. Privitera¹, T. Castellì¹, M. Madonia², S. La Vignera³, R. Condorelli³, A. E. Calogero³, F. P. Farina², S. Gimino¹ & G. Morgia¹

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