Acido ialuronico: Nuove frontiere nella rigenerazione cartilaginea

OSTEOARTROSI

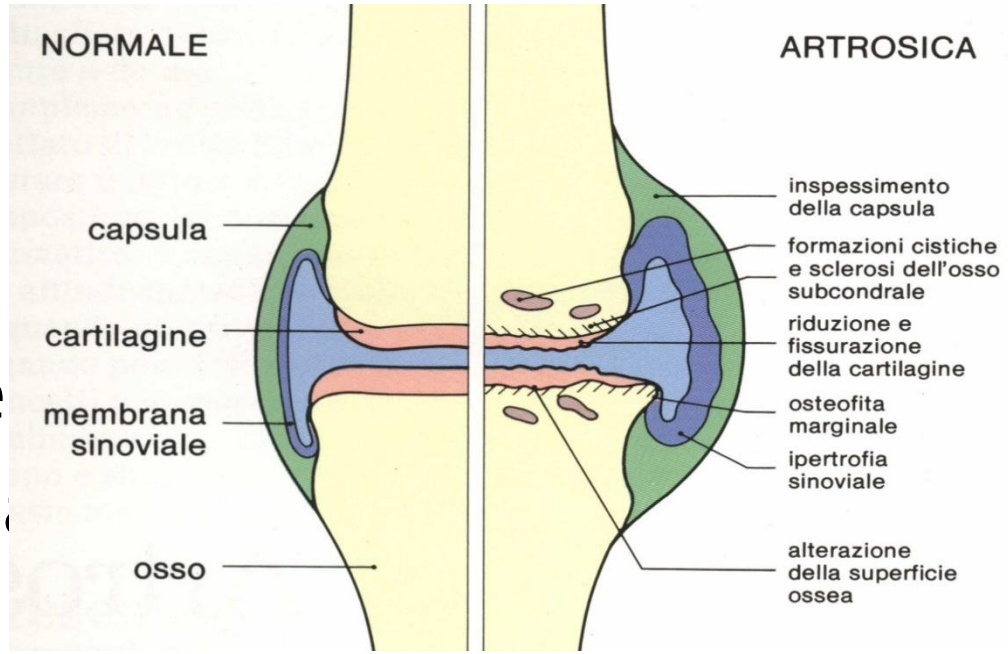
L'osteoartrosi è un processo patologico di natura degenerativa che trae origine dalla perdita dell'equilibrio fisiologico tra fenomeni catabolici e fenomeni riparativi a livello della cartilagine articolare.

Il processo coinvolge osso subcondrale e membrana sinoviale, determinando una alterazione articolare. Dal punto di vista clinico si manifesta sotto forma di dolore, deformità e disabilità. È una malattia correlata all'età, ma non è soltanto degli anziani, né colpisce tutti gli anziani

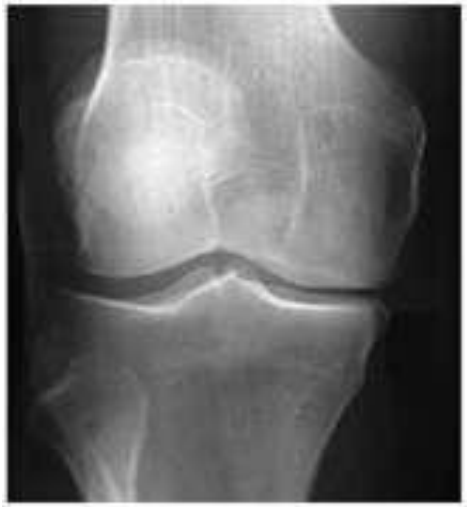
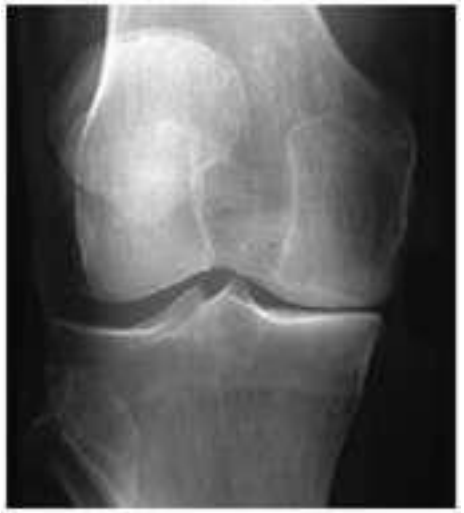
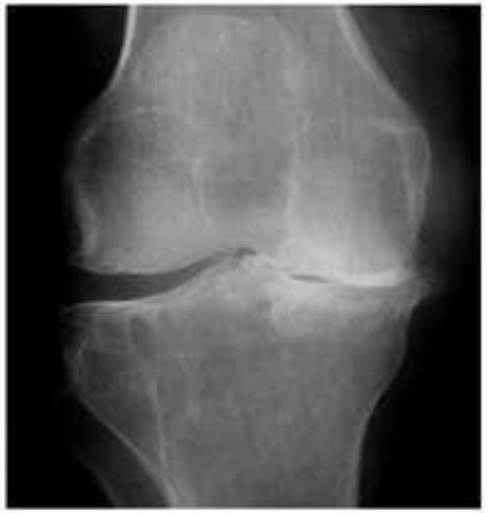
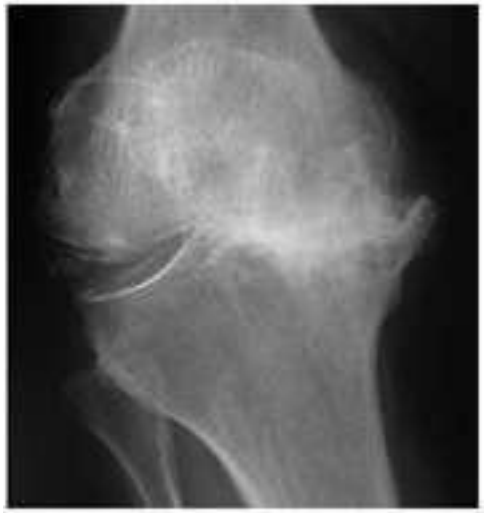
Arthritis & Reumatism 2000)

CAMBIAMENTI NELL'ARTROSI

- Dolore locale e rigidità
- Versamento articolare
- Deformità ed instabilità articolare
- Rammollimento e perdita di cartil
- Formazione di osteofiti
- Sbilanciamento tra processi di sintesi e di degradazione della cartilagine



TRATTAMENTO

TERAPIA MEDICA

1) Fast Acting Drugs for Osteoarthritis

-Analgesici

-FANS

-Corticosteroidi /
AI

2) Slow Acting Drugs for Osteoarthritis

-Condrointinsolfato

-Acido Ialuronico (AI)

-Glucosamina
solfato

(Lequense 1994)

CONDROPROTEZIONE IDEALE

- Mantenimento del metabolismo condrocitario
- Mantenimento delle proprietà del *liquido sinoviale*
- Inibizione dei processi degradativi della cartilagine
- Stimolazione della sintesi cartilaginea

ACIDO IALURONICO

Hyaluronans are polysaccharide molecules that occur naturally in synovial fluid; they help to
create a viscous environment, cushion joints, and maintain normal function

(Altman 2003)

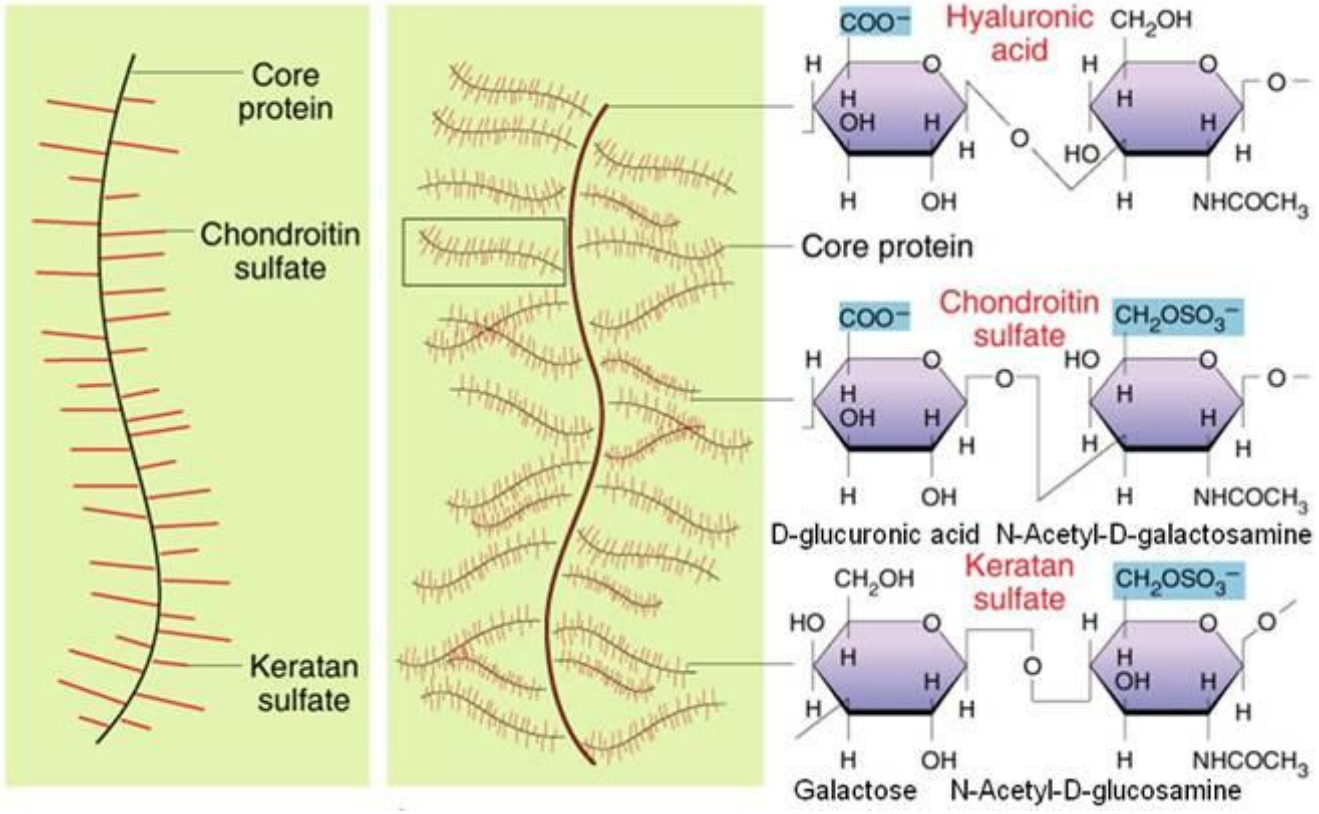
ACIDO IALURONICO

- Glicosaminoglicano lineare (N-acetilglucosamina-acido glicuronico)
- Identico tra le forme di vita
- Presente in elevate concentrazioni nei tessuti connettivali
- Massima concentrazione nel liquido sinoviale delle articolazioni diartroidali

(Altman 2004; Ghosh 2002)

ACIDO IALURONICO

- Sintetizzato dai sinoviociti di tipo B, garantisce l'attività di filtro della membrana sinoviale
- Bilancio idrico tissutale
- Interazioni steriche
- Lubrificazione



ACIDO IALURONICO

Sono disponibili di origine:

a) animale (creste di gallo ed occhi bovini)

b) da fermentazione batterica (pura sintesi)

Hanno tre categorie di peso molecolare medio: 500 Kdalton – 1.000 Kdalton – 6.000 Kdalton.

ACIDO IALURONICO

L’ Acido Ialuronico è il maggior responsabile delle caratteristiche viscoelastiche del liquido sinoviale

Il peso molecolare e la concentrazione di AI sono diminuiti nell’Osteoartrosi:

-Diminuzione in base alla diluizione

-Diminuzione dell’AI nel liquido sinoviale

-Alterata sintesi di AI

RUOLO DELL' ACIDO IALURONICO

NELLA CARTILAGINE:

-Inibisce la perdita dei proteoglicani contribuendo a mantenere l'omeostasi della matrice extracellulare

-Forma un rivestimento intorno ai condrociti, interagendo con specifici recettori modula la proliferazione, la migrazione e l'espressione genica condrocitaria

-L' AI di PM compreso tra 500 e 730 kd è in grado di rallentare l'apoptosi dei condrociti Fas mediata nell'OA legandosi al recettore CD44 e CD54

-Determina il turgore e la deformabilità delle cartilagini *(Altman 2004)*

RUOLO DELL' ACIDO IALURONICO

NEL LIQUIDO SINOVIALE:

- Riduce la perdita di liquidi in flessione
- Regola gli scambi di acqua e soluti tra i capillari, membrana sinoviale e liquido sinoviale
- Limita gli scambi di grosse proteine tra i compartimenti sopra citati
- Notevoli capacità viscoelastiche che aiutano le articolazioni nel sopportare i carichi meccanici
- Determina grossa resistenza agli stress articolari tangenziali

(Altman 2004)

RUOLO DELL’ ACIDO IALURONICO

NELLA MEMBRANA SINOVIALE:

-Funge da filtro tra il liquido emolinfatico e liquido sinoviale

-Controllo del movimento cellulare da e per la cavità articolare

-Effetto analgesico per la capacità di legare peptidi mediatori del dolore e/o per la capacità di interagire col loro recettore, CD44, posto sulle terminazioni nocicettive

-Protezione meccanica dei sinoviociti

(Gotoh 1993)

MECCANISMO D'AZIONE

-Protezione dalla perdita di proteoglicani

-Protezione dai radicali liberi dell'ossigeno

-Protezione dall'apoptosi Fas e NO mediata

-Modulazione dell'aderenza leucocitaria, proliferazione, migrazione e fagocitosi

-Inibizione della degradazione della matrice cartilaginea da parte della fibronectina

-Inibizione NO e PG

(Ghosh 2002)

FUNZIONE DELL’ AI: VISCOSUPPLEMENTAZIONE…

Il concetto della Viscosupplementazione si fonda sull’ipotesi che l’iniezione intra-articolare di AI aiuta a ristabilire la viscoelasticità del liquido sinoviale, aumentando la funzionalità articolare

J Rheumatol Suppl. 1993 Aug;39:3-9.

Viscosupplementation: a new concept in the treatment of osteoarthritis.

Balazs EA[1], Denlinger JL.

…E NON SOLO

Il beneficio delle iniezioni intra-articolari di Acido Ialuronico ben oltre l'emivita farmacologica del prodotto suggeriscono altri potenziali meccanismi:

Diminuzione del dolore

Miglioramento della funzione articolare

Potenziali effetti positivi sulle strutture articolari

-Viscoinduzione *(Balazs 1993, 2003; Frizziero 1998; Goldberg 2005; Kawasaki 1999)*

...E NON SOLO

Cells Tissues Organs. 2003;174(1-2):49-62.

Analgesic effect of elastoviscous hyaluronan solutions and the treatment of arthritic pain.

Balazs EA[1].

Clin Exp Rheumatol. 1998 Jul-Aug;16(4):441-9.

Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: clinical and morphological study.

Frizziero L[1], Govoni E, Bacchini P.

Osteoarthritis Cartilage. 2005 Mar;13(3):216-24.

Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity.

Goldberg VM[1], Buckwalter JA.

J Cell Physiol. 1999 May;179(2):142-8.

Hyaluronic acid enhances proliferation and chondroitin sulfate synthesis in cultured chondrocytes embedded in collagen gels.

Kawasaki K[1], Ochi M, Uchio Y, Adachi N, Matsusaki M.

VISCOINDUZIONE

Approccio terapeutico che si basa sull'iniezione intra-articolare di un determinato peso molecolare di HA Intra-articolare di un determinato peso molecolare di HA che è in grado di esplicitare attività farmacologica, in termini di neo-sintesi di HA fisiologico, oltre che a ristabilire le caratteristiche reologiche

VISCOINDUZIONE

- Inibizione della condrodegenerazione
- Stimolazione della crescita condrocitaria
- Inibizione dell'apoptosi condrocitaria
- Diminuzione dei processi infiammatori

(Goldberg 2005; Kawasaki

Osteoarthritis Cartilage. 2005 Mar;13(3):216-24.

Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity.

Goldberg VM[1], Buckwalter JA.

J Cell Physiol. 1999 May;179(2):142-8.

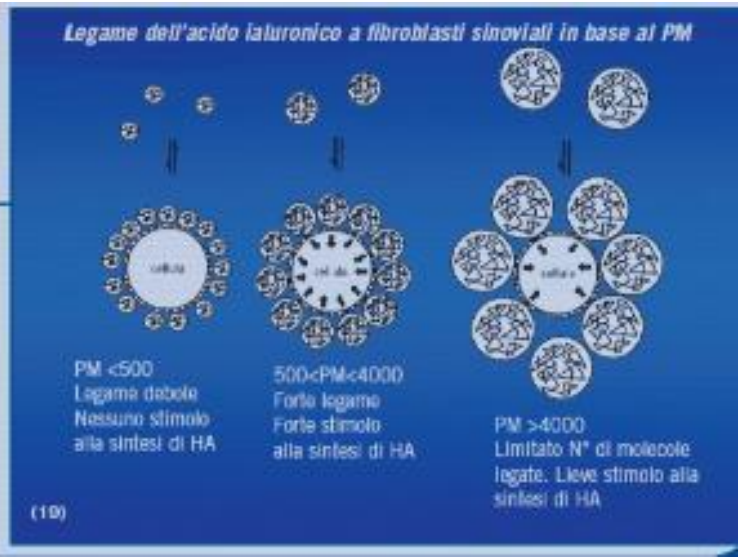
Hyaluronic acid enhances proliferation and chondroitin sulfate synthesis in cultured chondrocytes embedded in collagen gels.

Kawasaki K[1], Ochi M, Uchio Y, Adachi N, Matsusaki M.

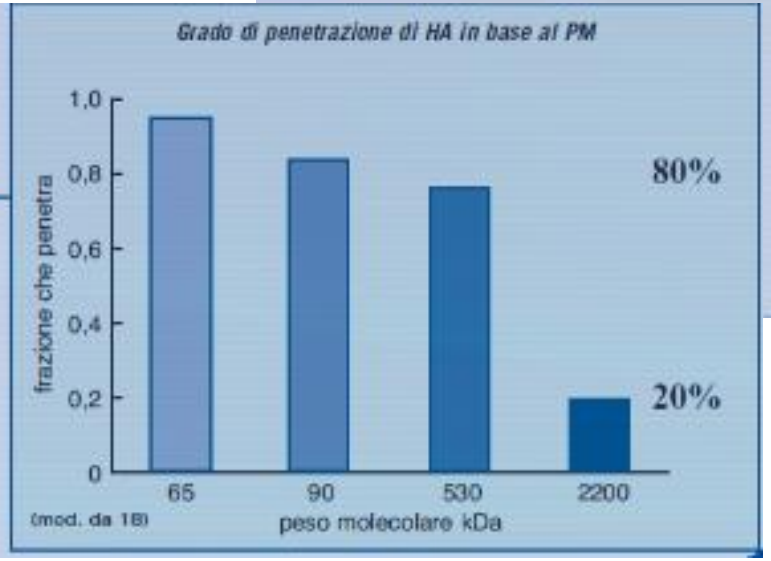
QUALE ACIDO IALURONICO USARE:

- L' Acido Ialuronico con PM compreso tra 500 e 730 KD sembrerebbe da preferirsi per il duplice effetto Meccanico/Biologico

Perchè sufficientemente grandi per interagire con i recettori cellulari. (17)



Perché abbastanza piccole per penetrare nella membrana sinoviale... (17)



QUALE ACIDO IALURONICO USARE:

- Studi in vivo hanno dimostrato il maggior effetto protettivo dell'acido ialuronico a basso/medio PM

- L'AI a basso peso molecolare dimostra una maggior capacità penetrativa all'interno dei tessuti, potendosi meglio distribuire intorno le strutture cellulari

- L'AI ialuronico con PM tra 500-730 KD è in grado di interagire con i recettori cellulare CD44 e CD54 stimolando quelle risposte biologiche alla base della condroprotezione e inibizione apoptotica condrocitaria

INOLTRE…

(Altman 2004; Ghosh 2002)

QUALE ACIDO IALURONICO USARE:

…RUOLO SULL'INFIAMMAZIONE:

- L' AI con PM tra i 500 e 1000 KD è più efficace nel diminuire gli indici infiammatori sinoviale
- L' AI a basso PM riduce gli effetti di IL-1 sulla sintesi di PG2 e NO
- L' AI a basso PM risulta avere una miglior capacità di ridurre l'apoptosi cellulare NO mediata

(Morris 2001; Maniero et al. 2004)

INDICAZIONI

-Dolore persistente, già trattato con altre terapie farmacologiche e non, in artrosi radiologicamente moderata con modesto o assente versamento articolare

-Trattamento di secondo livello dopo una pregressa sinovite

-Artrosi dolorosa in caso di rifiuto di intervento chirurgico protesico o controindicazione allo stesso

-In caso di controindicazione o rifiuto alla terapia farmacologica con analgesici o FANS

Tuttavia…

INDICAZIONI

… Ancora non ci sono indicazioni univoche sull'utilizzo dell' AI nell' OA

Am Fam Physician. 2000 Aug 1;62(3):565-70, 572.

Intra-articular hyaluronic acid injections for knee osteoarthritis.

Wen DY[1].

⊕ **Author information**

Abstract

Knee osteoarthritis is a common but often difficult problem to manage in primary care. Traditional nonsurgical management, consisting of lifestyle modification, physical therapy and pharmacologic therapy (e.g., analgesics, anti-inflammatory medications), is often ineffective or leaves residual symptoms. Viscosupplementation is a newly available option for patients with symptomatic knee osteoarthritis that involves a series of intra-articular injections of hyaluronic acid. The exact mechanism of action is unclear, although increasing the viscoelasticity of the synovial fluid appears to play a role. Clinical experience and studies of the two hyaluronic acid products available, hyaluronan and hylan G-F 20, are inconclusive but seem to indicate beneficial effects with minimal adverse reactions in a significant number of patients. The exact indications for viscosupplementation are still evolving, but it currently can be considered for use in patients who have significant residual symptoms despite traditional nonpharmacologic and pharmacologic treatments. In addition, patients who are intolerant of traditional treatments (e.g., gastrointestinal problems related to anti-inflammatory medications) can be considered for these injections. Family physicians with the ability to perform intra-articular knee injections should consider them an option in patients with symptomatic knee osteoarthritis.

INDICAZIONI

Contrastanti risultati nei casi di artrosi severa

Int J Clin Pract. 2003 Jul-Aug;57(6):467-74.

A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee.

Jubb RW[1], Piva S, Beinat L, Dacre J, Gishen P.

Author information

Abstract

The primary objective of this study was to investigate structural changes, as measured by joint space narrowing (JSN), within the knee joint during treatment with intra-articular sodium hyaluronate (HA) of molecular weight 500-730 kDa in patients with osteoarthritis (OA) of the knee. Patients received a weekly intra-articular injection of either 20 mg2/ml HA or a 2 ml vehicle placebo (saline) for three weeks. This course was repeated twice more at four-monthly intervals. Concomitant treatment with analgesics or NSAIDs was allowed. The primary efficacy measure was the reduction in mean joint space width (JSW) of the medial compartment at 52 weeks. A total of 408 patients were randomised and 319 completed the one-year study (HA: n=160, placebo: n=159); 273 of the 319 were included in the primary analysis. Analysis of variance on these 273 patients did not show a statistically significant difference between the two treatment groups. However, there was a significant difference in response to treatment in terms of the baseline JSW (p=0.01), indicating that outcome of treatment may depend on-baseline JSW. Therefore, a subgroup analysis by baseline JSW was conducted. This compared patients with a JSW >4.6 mm with those with a JSW <4.6 mm. In those with radiologically milder disease at baseline and receiving HA, the JSN was significantly reduced compared with placebo (p=0.02). In patients with radiologically more severe disease there was no difference in JSN between the two treatments. Although, in this one-year study, no overall treatment effect was seen, those with radiologically milder disease at baseline had less progression of joint space narrowing when treated with HA.

PMID: 12918884 [PubMed - indexed for MEDLINE]

INDICAZIONI

Orthop Traumatol Surg Res. 2015 Feb;101(1 Suppl):S101-8. doi: 10.1016/j.otsr.2014.07.027. Epub 2015 Jan 14.

Viscosupplementation: techniques, indications, results.

Legré-Boyer V[1].

related chondropathy has yet to be properly assessed. The optimal response profile remains to be determined. The ideal indication in the knee seems to be moderate femorotibial OA without swelling. Results have been generally disappointing in hip osteoarthritis but promising in OA of the ankle and

CONTROINDICAZIONI

- Infezioni locale o sistemica
- Terapia anticoagulante
- Diatesi emorragica
- Ipersensibilità al principio attivo
- Versamento articolare*

SCHEMA TERAPEUTICO

- Per i preparati a basso PM (<1000 KD), a causa della breve permanenza del prodotto all'interno del liquido sinoviale (circa 24 h) si consigliano iniezioni ripetute settimanalmente per un totale di 3-5 settimane
- Per i preparati a medio/alto PM (>2000/3500 KD), data la loro più lenta degradazione intra-articolare e la più lunga emivita farmacologica (circa 4 settimane), è possibile iniettare una singola dose per ottenere risultati duraturi

(Altman 2002; Lindqvist 2002)

DURATA D'AZIONE

J Pain Res. 2015 May 7;8:217-28. doi: 10.2147/JPR.S83076. eCollection 2015.

Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials.

Strand V[1], McIntyre LF[2], Beach WR[3], Miller LE[4], Block JE[5].

Author information

Abstract

BACKGROUND: Intra-articular injection of hyaluronic acid is a common, yet controversial, therapeutic option for patients with knee osteoarthritis (OA). The purpose of this research was to determine the safety and efficacy of US-approved viscosupplements for symptomatic knee OA.

METHODS: We searched MedLine and EMBase for randomized, sham-controlled trials evaluating safety and/or clinical efficacy of US-approved viscosupplements in patients with symptomatic knee OA. Knee pain severity and knee joint function were assessed at 4 to 13 weeks and 14 to 26 weeks. Safety outcomes included serious adverse events, treatment-related serious adverse events, patient withdrawal, and adverse event-related patient withdrawal occurring at any time during follow-up.

RESULTS: A total of 29 studies representing 4,866 unique patients (active: 2,673, control: 2,193) were included. All sham-controlled trials used saline injections as a control. Viscosupplementation resulted in very large treatment effects between 4 and 26 weeks for knee pain and function compared to preinjection values, with standardized mean difference values ranging from 1.07 to 1.37 (all $P<0.001$). Compared to controls, standardized mean difference with viscosupplementation ranged from 0.38 to 0.43 for knee pain and 0.32 to 0.34 for knee function (all $P<0.001$). There were no statistically significant differences between viscosupplementation and controls for any safety outcome, with absolute risk differences of 0.7% (95% confidence interval [CI]: -0.2 to 1.5%) for serious adverse events, 0% (95% CI: -0.4 to 0.4%) for treatment-related serious adverse events, 0% (95% CI: -1.6 to 1.6%) for patient withdrawal, and 0.2% (95% CI: -0.4 to 0.8%) for adverse event-related patient withdrawal.

CONCLUSION: Intra-articular injection of US-approved viscosupplements is safe and efficacious through 26 weeks in patients with symptomatic knee OA.

RISULTATI: HA SI…

Viscosupplementation for the treatment of osteoarthritis of the knee

Nicholas Bellamy[1,*], Jane Campbell[2], Vivian Welch[3], Travis L Gee[4], Robert Bourne[2], George A Wells[5]

Editorial Group: Cochrane Musculoskeletal Group

Published Online: 19 APR 2006

Assessed as up-to-date: 21 FEB 2006

DOI: 10.1002/14651858.CD005321.pub2

Database Title

The Cochrane Library

Authors' conclusions

Based on the aforementioned analyses, viscosupplementation is an effective treatment for OA of the knee with beneficial effects: on pain, function and patient global assessment; and at different post injection periods but especially at the 5 to 13 week post injection period. It is of note that the magnitude of the clinical effect, as expressed by the WMD and standardised mean difference (SMD) from the RevMan 4.2 output, is different for different products, comparisons, timepoints, variables and trial designs. However, there are few randomised head-to-head comparisons of different viscosupplements and readers should be cautious, therefore, in drawing conclusions regarding the relative value of different products. The clinical effect for some products, against placebo, on some variables at some timepoints is in the moderate to large effect-size range. Readers should refer to relevant tables to review specific detail given the heterogeneity in effects across the product class and some discrepancies observed between the RevMan 4.2 analyses and the original publications. Overall, the analyses performed are positive for the HA class and particularly positive for some products with respect to certain variables and timepoints, such as pain on weight bearing at 5 to 13 weeks postinjection.

In general, sample-size restrictions preclude any definitive comment on the safety of the HA class of products; however, within the constraints of the trial designs employed no major safety issues were detected. In some analyses viscosupplements were comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events.

In other analyses HA products had more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.

RISULTATI: …HA SI…

Arthroscopy. 2015 May 18. pii: S0749-8063(15)00257-1. doi: 10.1016/j.arthro.2015.03.030. [Epub ahead of print]

Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses.

Campbell KA[1], Erickson BJ[2], Saltzman BM[2], Mascarenhas R[3], Bach BR Jr[2], Cole BJ[2], Verma NN[2].

Author information

Abstract

PURPOSE: To conduct a systematic review of overlapping meta-analyses comparing treatment of knee osteoarthritis (OA) with intra-articular viscosupplementation (intra-articular hyaluronic acid [IA-HA]) versus oral nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids (IA-corticosteroids), intra-articular platelet-rich plasma (IA-PRP), or intra-articular placebo (IA-placebo) to determine which meta-analyses provide the best current evidence and identify potential causes of discordance.

METHODS: Literature searches were performed for meta-analyses examining use of IA-HA versus NSAIDs, IA-corticosteroids, IA-PRP, or IA-placebo. Clinical data were extracted, and meta-analysis quality was assessed. The Jadad algorithm was applied to determine which meta-analyses provided the highest level of evidence.

RESULTS: Fourteen meta-analyses met the eligibility criteria and ranged in quality from Level I to IV evidence. In studies reporting patient numbers, there were a total of 20,049 patients: 13,698 receiving IA-HA, 355 receiving NSAIDs, 294 receiving IA-corticosteroids, and 5,702 receiving IA-placebo. Ten studies examined the effects of IA-HA versus IA-placebo; of these, 5 found that IA-HA improved pain and 4 found that IA-HA improved function. No clinically relevant differences in the efficacy of IA-HA versus NSAIDs regarding pain and function were found. Regarding IA-HA versus IA-PRP, IA-HA improved knee function at 2 and 6 months after injection but the effects were less robust than those of IA-PRP. Regarding IA-HA versus IA-corticosteroids, the positive effects of IA-HA were greater at 5 to 13 weeks and persisted for up to 26 weeks. After application of the Jadad algorithm, 2 concordant high-quality meta-analyses were selected and both showed that IA-HA provided clinically relevant improvements in pain and function compared with IA-placebo.

CONCLUSIONS: This systematic review of overlapping meta-analyses comparing IA-HA with other nonoperative treatment modalities for knee OA shows that the current highest level of evidence suggests that IA-HA is a viable option for knee OA. Its use results in improvements in knee pain and function that can persist for up to 26 weeks. IA-HA has a good safety profile, and its use should be considered in patients with early knee OA.

LEVEL OF EVIDENCE: Level IV, systematic review of Level I to IV studies.

RISULTATI: HA NO…

Ann Intern Med. 2012 Aug 7;157(3):180-91. doi: 10.7326/0003-4819-157-3-201208070-00473.

Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis.

Rutjes AW[1], Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S.

⊕ Author information

Abstract

BACKGROUND: Viscosupplementation, the intra-articular injection of hyaluronic acid, is widely used for symptomatic knee osteoarthritis.

PURPOSE: To assess the benefits and risks of viscosupplementation for adults with symptomatic knee osteoarthritis.

DATA SOURCES: MEDLINE (1966 to January 2012), EMBASE (1980 to January 2012), the Cochrane Central Register of Controlled Trials (1970 to January 2012), and other sources.

STUDY SELECTION: Randomized trials in any language that compared viscosupplementation with sham or nonintervention control in adults with knee osteoarthritis.

DATA EXTRACTION: Primary outcomes were pain intensity and flare-ups. Secondary outcomes included function and serious adverse events. Reviewers used duplicate abstractions, assessed study quality, pooled data by using a random-effects model, examined funnel plots, and explored heterogeneity by using meta-regression.

DATA SYNTHESIS: Eighty-nine trials involving 12 667 adults met inclusion criteria. Sixty-eight had a sham control, 40 had a follow-up duration greater than 3 months, and 22 used cross-linked forms of hyaluronic acid. Overall, 71 trials (9617 patients) showed that viscosupplementation moderately reduced pain (effect size, -0.37 [95% CI, -0.46 to -0.28]). There was important between-trial heterogeneity and an asymmetrical funnel plot: Trial size, blinded outcome assessment, and publication status were associated with effect size. Five unpublished trials (1149 patients) showed an effect size of -0.03 (CI, -0.14 to 0.09). Eighteen large trials with blinded outcome assessment (5094 patients) showed a clinically irrelevant effect size of -0.11 (CI, -0.18 to -0.04). Six trials (811 patients) showed that viscosupplementation increased, although not statistically significantly, the risk for flare-ups (relative risk, 1.51 [CI, 0.84 to 2.72]). Fourteen trials (3667 patients) showed that viscosupplementation increased the risk for serious adverse events (relative risk, 1.41 [CI, 1.02 to 1.97]).

LIMITATIONS: Trial quality was generally low. Safety data were often not reported.

CONCLUSION: In patients with knee osteoarthritis, viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events.