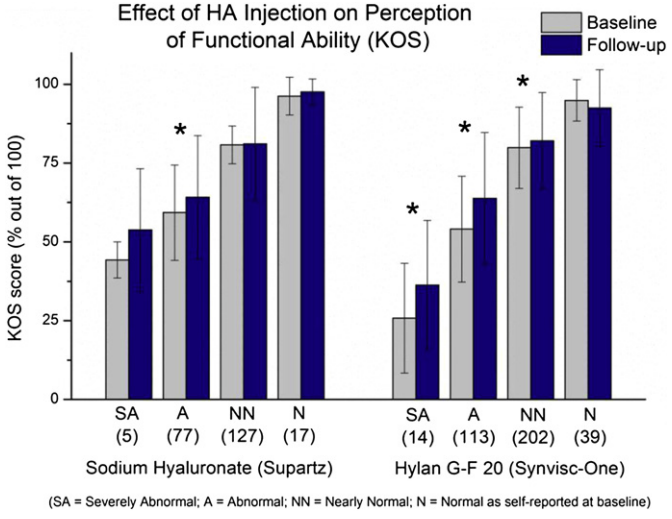
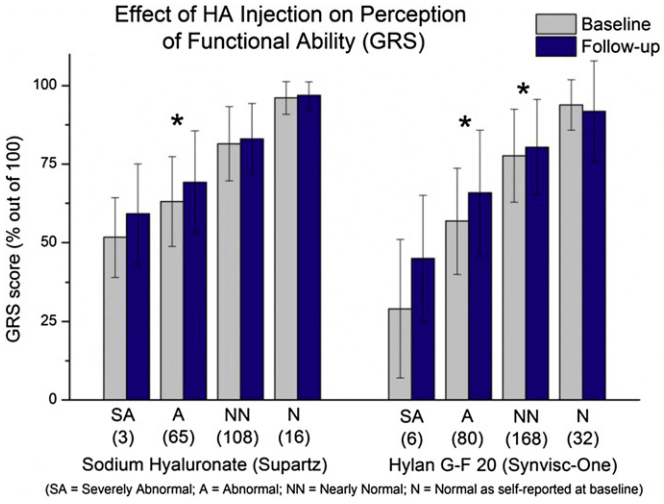
not all patients that receive HA injections have an optimal response. Several different HA formulations are available and a comparative analysis of outcomes is lacking in the literature. Therefore, the purpose of this study was to quantify the functional benefit of two different HA formulations for individuals with knee OA.

Methods: The Knee Outcome Survey (KOS) and Global Rating Score (GRS) from patients who received HA injections for knee OA were analyzed. Patients with bilateral injections completed a questionnaire for each limb. Baseline KOS and GRS scores prior to injection and scores 4-6 weeks after the last injection were compared between subjects who received 5 Sodium Hyaluronate (Supartz) injections (n = 226) or a single Hylan G-F 20 (Synvisc-One) injection (n = 368). "Responders" to the HA injections were operationally defined as 1) Patients who had a KOS change score greater than 10 points or 2) Patients who showed any increase in KOS scores. Self-reported knee function, ranked as "Severely Abnormal", "Abnormal", "Nearly Normal", or "Normal" was evaluated at baseline to stratify groups if a significant interaction effect was found. "Normal" subjects were subjects without functional limitations, but may have had pain or were known to have chondral lesions. A repeated measures ANOVA was used to assess change in KOS score between injection types and over time. Chi-square analysis was used to determine differences in the responder rate between injection types and determine if there was a relationship between change perception of function (KOS and GRS) and baseline self-reported knee function.

Results: 594 knees were assessed and time between first injection and follow-up was 78 +/- 13 days for patients who received Sodium Hyaluronate and 46 +/- 15 days for patients who received Hylan G-F 20. There was a significant Self-Function by Time interaction effect ($p \leq 0.002$) and those with lower reported self-functional score (abnormal, severely abnormal) demonstrated greater improvement in KOS and GRS scores at follow-up (Figures 1 and 2). There was no Injection Type by Time interaction effect and no difference in responder rates when stratified by injection type suggesting no difference in outcomes between the multi or single injection ($p > 0.455$). Most patients patients demonstrated some improvement on the KOS at follow-up, although a smaller number of individuals achieved a 10 point change on the KOS (Table 1).

Conclusions: HA injections offer small, but significant improvements in self-reported function for the majority of patients with OA. There was no additional functional benefit to using one particular formulation. Patients who report their knee function as abnormal or severely abnormal at baseline are most likely to have a larger response at follow-up. Future evaluations should assess pain and performance in addition to self-perception outcomes.





Number of Responders to HA injection by Injection Type and Baseline Self-reported Knee Function

	Self-reported knee function as recorded at baseline	N	No. of Responders (> 10 point KOS Change)	Percentage Responders (%)	No. of Responders (Any KOS Increase)	Percentage Responders (%)
Sodium Hyaluronate	Severely Abnormal	5	2	40.00	4	80.00
	Abnormal	77	30	38.96	49	63.64
	Nearly Normal	127	21	16.54	68	53.54
	Normal	17	0	0.00	6	35.29
Hylan G-F 20	Severely Abnormal	14	6	42.86	12	85.71
	Abnormal	113	46	40.71	85	75.22
	Nearly Normal	202	36	17.82	121	59.90
	Normal	39	0	0.00	16	41.03

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INTRA ARTICULAR DRUG DELIVERY THROUGH AN *IN-SITU* GELLING SYSTEM

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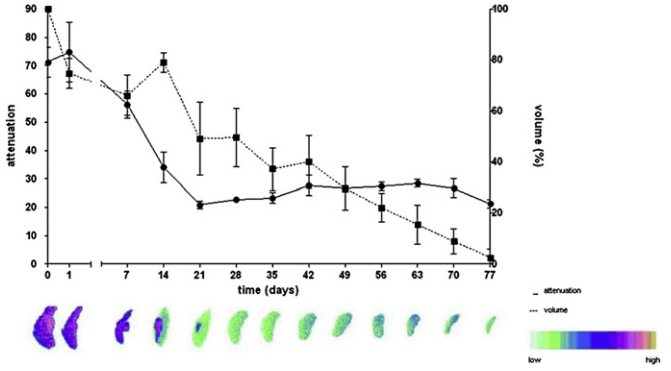
Purpose: Our aim was to develop a biodegradable, *in situ* forming gel suitable for prolonged, i.e. several weeks, intra-articular drug delivery. Gel degradation kinetics, visualization, drug release and intra-articular biocompatibility were tested

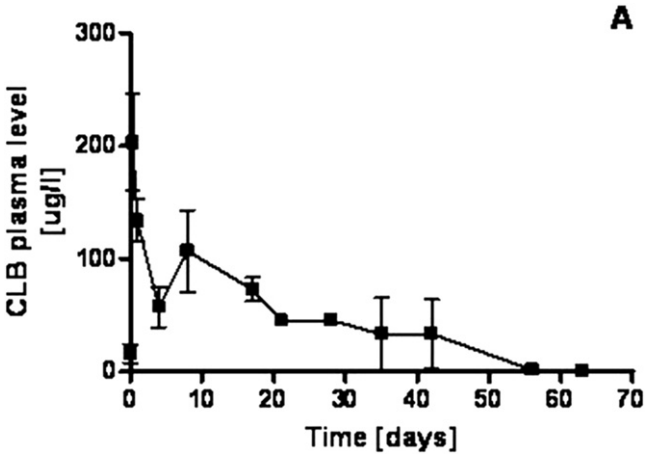
Methods: Gel synthesis PCLA-PEG-PCLA synthesis was performed by ring opening polymerization of L-lactide and ε-caprolactone in solution using PEG1500-diol as macroinitiator and tin(II) 2-ethylhexanoate as catalyst. To gain radiopacity, TIBO-capping of the PCLA-PEG-PCLA was perfomed using an excess of TIBO chloride. *In-vitro* gel behavior Phosphate buffer was added to the polymer (25wt %) and the resulting gel was kept at 37 °C for the duration of the experiment. At predetermined time points, residual gel weight was measured. *In-vivo* experiments Group 1 (*n=6 male Wistar rats*); 100µl radiopaque gel was injected subcutaneous (n=4) or in the knee joint (n=2) and scanned regularly to visualize *in vivo* gel degradation longitudinally. Attenuation and volume of the gels were calculated. Group 2 *(n=10);* 50 µl non-radiopaque gel was injected in the left knee, the right knee served as a control (50µl saline). µCT arthographies were acquired before injection, after 6 and 12 weeks to monitor cartilage quality (sGAG content is correlated inversely to Hexabrix influx) and quantity over time. After the last scan, knees were harvested for histology. Group 3 (n=5); 500 µl of Celecoxib loaded gels (60 mg/g) were injected subcutaneously and blood samples were taken regularly to analyze drug release with UPLC.

Results: In-vitro gel degradation Complete gel degradation took ~130-140 days. Gel attenuation corresponded well with the measured polymer concentration over time, proving that µCT is indeed a good technique to quantify the amount of polymer present. In-vivo experiments Group 1: Total gel volume directly after subcutaneous injection by µCT was set at 100% and for all following time points the percentage of residual volume was calculated (figure 1). A controlled degradation was observed for period of twelve weeks. Upon intra-articular injection, the

gel was contained within the knee while slowly degrading over a period of 4 weeks. Group 2: No changes in patellar cartilage quantity or quality occurred following intra-articular gel injection ($p>0.10$). At t=0; t=6weeks and t=12weeks, cartilage volume L/R ratios were 1.02±0.12; 0.99±0.1; 1.08±.04 respectively; for attenuation 1.04±0.09; 1.05±0.08; 1.03±0.13. Histology confirmed that the gel did not affect the cartilage. Group 3; sustained drug release from the gel was confirmed with Celecoxib being detectable in plasma samples up to 40 days at a sustained level of ~50-100 ìg/l (figure 2).

Conclusions: Aliphatically-modified PCLA-PEG-PCLA form radiopaque and biocompatible gels which are able to deliver encapsulated drugs upon degradation over a period of several weeks. This system is therefore a promising candidate for intra articular drug delivery as a treatment for OA.





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SAFETY OF MULTIPLE MUSCULOSKELETAL INJECTIONS IN PATIENTS TAKING WARFARIN OR WARFARIN AND ASPIRIN

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Purpose: Injections involving the musculoskeletal system are a common practice in rheumatology. Several studies have shown the relative safety of single musculoskeletal injections (MSI) in patients taking warfarin. This prospective study looked at repeated injections regarding the ongoing safety of MSI in patients taking warfarin and also in patients taking warfarin and low dose aspirin.

Methods: A total of 42 patients were entered into the study from 1/2008 to 12/2010. There were a total of 216 injections. All patients who had at least 2 MSI in any part of their musculoskeletal system and were actively followed in the VA Anticoagulation Clinic were included in the study. Patients who received only one MSI or had multiple injections but were not followed by the VA Anticoagulation Clinic during the study period were excluded. All of the patients were taking warfarin and 14 were also taking aspirin for a variety of causes. All patients were on stable doses of warfarin and had INR levels within a month of the injections. After receiving injections, all patients were contacted by phone within a month of the injections, at the time of the INR check, and directly asked if there had been any complications related to the injections.

Results: Of the 216 injections in the 42 patients, the knee was the most common joint injected (n = 91: 42.1%). Other sites of injections included the shoulder (n = 56: 25.9%); humeral epicondyle (n = 6: 2.7%); small hand joints (n = 11: 5.1%); wrist (n = 5: 2.3%); various bursae (n = 14: 6.5%); other soft tissue sites (n = 33: 15.2%) Injectates included corticosteroids (CS) and hyaluronate. CS injections were the most common representing 81.8% of the total injections .The average total number of injections per patient was 5.1. The mode was 2. INR levels ranged from 1.1 - 4.8; average INR: 2.5. Only two patients reported bruising at the injection site. One patient was also taking aspirin. INRs in both patients were 2.1 and 2.4. No other complications were reported and no added complications in the patients taking both warfarin and aspirin.

Conclusions: It has been shown that single MSI are safe in patients on warfarin. This study demonstrates that repeated injections in any site in the musculoskeletal system are also safe in patients on warfarin and patients on warfarin and aspirin.

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AN INNOVATIVE HYALURONIC ACID PRODUCT FOR VISCOSUPPLEMENTATION IN PATIENTS WITH OSTEOARTHRITIS

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Purpose: The specific formulation [HA+sorbitol] of Synolis™ V-A is based on a high molecular weight of HA (> 2 MDa in the final sterilized gel) from non animal origin, with a high HA concentration (20 mg/ml), combined with a high concentration of a free radical scavenger, the sorbitol (40 mg/ml). The aims of this study are to evaluate the mechanical/rheological properties and the resistance to free radicals degradation of Synolis™ V-A.

Methods: The rheological properties are analyzed by frequency sweep experiments at 25°C thanks to a parallel plate rheometer (AR2000, TA Instruments). The resistance to free radical degradation is observed visually by adding an oxidant agent (H2O2) on the viscosupplement (Weight of H2O2 = 1/15 x Weight of viscosupplement), by heating the mixing at 60°C and by watching the flow of the product over time. The resistance to free radical degradation is also followed thanks to an AR2000 rheometer (time sweep experiments at 37°C). Results of resistance to degradation obtained with Synolis V-A are compared to 5 other commercial viscosupplements.

Results: Visco-elastic properties of Synolis V-A. Synolis V-A is characterized by a visco-elastic behavior close to the human synovial fluid (viscous and elastic moduli crossing at 0.4 Hz) and high viscous and elastic moduli due to the high affinity between HA and sorbitol that stabilizes the structure through a very dense network of hydrogen bonds. Resistance to free radical degradation. In presence of free radicals (H2O2), Synolis V-A demonstrates a much higher resistance against free radicals than the other commercial viscosupplements as shown by the visual observation and by the rheological properties.

Conclusions: Synolis V-A is an innovative viscosupplement made of hyaluronic acid and sorbitol. Due to its patented formulation and manufacturing process, Synolis V-A has outstanding rheological properties and a high resistance against in vivo degradation in the joint. As demonstrated by several experiments, Synolis V-A is characterized by a visco-elastic behaviour close to the human synovial fluid, a very high elasticity and viscosity and a high resistance to free radical degradation. The synergetic combination of HA of high molecular weight and sorbitol, combined with a specific manufacturing process which included a final moist heat sterilization, allows to obtain unique properties. Moreover, due to the high affinity between HA and sorbitol, Synolis V-A is stabilized through a very dense network of hydrogen bonds. This complex structure of gel presents remarkably high visco-elastic properties. Consequently, thanks to these particular visco-elastic properties, Synolis V-A has a high ability to lubricate joints and to absorb shocks, as with a healthy synovial fluid. On the other hand, the high ability of sorbitol to scavenge and neutralize free radicals (= antioxidant effect) allows to limit the degradation of the gel in order to increase the half-life of the product in the joint (as described in the