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A prospective comparison of the GOLDIC® technique and corticosteroid plus hyaluronic acid injections for arthrogenic lameness in horses

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Summary: Osteoarthritis is one of the most common causes of lameness and often is a career-ending disease in horses. Treatment of osteoarthritis is usually symptomatic and aimed at controlling the inflammation, either systemically or intra-articularly. Common intra-articular treatments include corticosteroids combined with hyaluronic acid and chondroprotective drugs such as glucosamine and chondroitin. The application of gold compounds, either orally or intramuscularly, has been used therapeutically for many decades, primarily in human patients with rheumatoid arthritis. Gold compounds (aurothiomalate) inhibit the production of nitric oxide (NO) of chondrocytes. Nitric oxide mediates the destructive effects of IL-1 and TNF, which include reduced collagen and proteoglycan production, apoptosis of chondrocytes and stimulation of metalloproteases. The purpose of the present study was to compare the efficacy of the GOLDIC® treatment with that of corticosteroids and hyaluronic acid in horses with arthrogenic lameness. A prospective randomized controlled, two-centre clinical trial was performed. 30 horses with arthrogenic lameness were enrolled in this study. The horses were treated by four injections of gold-induced, autologous conditioned serum GOLDIC® (group B, n = 16) or by a single injection of corticosteroid and hyaluronic acid (group A, n = 14). Lameness was assessed using the AAEP *Grading* system before and 3, 6, 12 and 36 months after treatment. The AAEP grade was the primary endpoint. Differences were considered significant at $P < 0.05$. Secondary endpoints were the results of the flexion test, degree of joint-effusion, radiographic findings, the ability to return to original performance level and adverse effects. Horses of group B had significantly lower lameness grades at the follow-up examinations compared with the value before treatment ($p < 0.01$). Both treatment groups showed positive effects on the AAEP-Score. Group B (Goldic®) showed much faster effect on the AAEP-Score. Also in the long run group B (Goldic®) showed a larger effect on the AAEP-Score. Severe side effects did not occur in either group. It has been shown that the treatment of arthrogenic lameness in horses with the gold-induced, autologous conditioned serum method (GOLDIC®) is in certain cases a promising alternative to conventional treatment with corticosteroids and hyaluronic acid.

Keywords: horse, lameness, osteoarthritis, Gold-induced, autologous conditioned serum, GOLDIC®, corticosteroid, hyaluronic acid, IRAP (interleukin-1 receptor antagonist protein), Orthokine, PRP (platelet-rich plasma)

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Introduction

Degenerative joint disease is very common in humans and in horses (*Rossdale* et al. 1985, *Lawrence* et al. 1998, *Johnston* 1997). In humans, osteoarthritis frequently occurs in elderly patients, but also in young people as a post-traumatic complication (*Buckwalter* 2003, *Buckwalter* and *Brown* 2004). The latter is also a problem in horses because osteoarthritis effects primarily sports horses (*McIlwraith* 1996). Joint pain impairs normal joint function and severely restricts the quality of life in human and equine patients (*Lawrence* et al. 1998). Osteoarthritis is one of the most common causes of lameness and often is a career-ending disease in horses (*Rossdale* et al. 1985), even more so than fatal fractures (*Cruz* and *Hurtig* 2008, *Pool* and *Meagher* 1990). Abnormal weight-bearing, joint instability and joint infection lead to mechanical and enzymatic damage to the joint cartilage with apoptosis of chondrocytes and loss of type II collagen and proteoglycans (*McIlwraith* 1996, *Lukoschek* et al. 1986, *Simmons* et al. 1999, *Norrdin* et al. 1998, *Green* et al. 2006, *Guilak* et al. 2004, *Buckwalter* 1995). Although the main component of the pathogenesis of osteoarthritis is the degeneration of the joint cartilage, the joint capsule and the subchondral bone are also affected (*McIlwraith* 1996, *Cruz* and *Hurtig* 2008, *Young* et al. 2007). The subchondral bone becomes denser than normal and sclerotic because of large cyclic loads that lead to impaired shock absorption. In addition, shear forces occur at the interface between the subchondral bone plate and mineralised cartilage (*McIlwraith* 1996, *Cruz* and *Hurtig* 2008, *Radin* and *Rose* 1986).

The synovial fluid of horses with chronic joint disease has higher levels of tumour necrosis factor (TNF), interleukin 1 (IL-1), IL-6 and prostaglandin E2 (PGE2) than normal horses

(*Bertone* et al. 2001). The same pro-inflammatory cytokines are also elevated in people with osteoarthritis (*Kobayashi* et al. 2005). Inflammatory cells of the synovial membrane, synoviocytes and chondrocytes secrete cytokines (*Spiers* et al. 1994, *Clegg* et al. 1997a, *Clegg* et al. 1997b, *David* et al. 2007, *Samuels* et al. 2008, *Goldring* et al. 1988, *Loeser* 2006, *Bondeson* et al. 2006) and stimulate the release of metalloproteinase (MMO's) and aggrecanasis (*Bondeson* et al. 2006), as well as other inflammatory mediators like prostaglandins (PGE2) or nitric oxide (NO) (*Guilak* et al. 2004, *Pelletier* et al. 2001, *von Rechenberg* et al. 2000).

Treatment of osteoarthritis is usually symptomatic and aimed at controlling the inflammation, either systemically or intra-articularly (*Caron* 2005, *Fortier* 2005). Common intra-articular treatments include corticosteroids combined with hyaluronic acid (*Frean* et al. 2002, *Schaefer* et al. 2009, *Trotter* 1996) and chondroprotective drugs such as glucosamine and chondroitin (*Frean* et al. 2002, *Frisbie* et al. 2009). Intra-articular injection of cytokine inhibitors, which include interleukin 1 receptor antagonists (IL-1Ra) have been used successfully in horses with osteoarthritis (*Frisbie* et al. 2007) and in humans with osteoarthritis and rheumatoid arthritis (*Baltzer* et al. 2003, *Baltzer* et al. 2009, *Bresnihan* et al. 1998). Orthokine/IRAP therapy involves the intra-articular injection of autologous conditioned serum in which the natural components that block interleukin-1 have been amplified. Incubation of autologous venous blood with chrome sulphate-impregnated glass pearls was shown to amplify the production of anti-inflammatory mediators (*Meijer* et al. 2003). However, the study by *Warner* et al. questions the long-term therapeutic success of this treatment (*Warner* et al. 2016). Another treatment approach is the intraarticular application of Polyacrylamide hydrogel (PAAHG). With this therapy, promising results in the treatment of osteoarthritis of the distal interphalangeal joint could be achieved (*Janssen* et al. 2012).

The application of gold compounds, either orally or intramuscularly, has been used therapeutically for many decades (*Jaeger* et al. 2006, *Schneider* 2011, *Schneider* and *Veith* 2013), primarily in human patients with rheumatoid arthritis. Currently, gold salts are administered subcutaneously in the form of gold sticks, and the newest form, termed extra-corporal inductive therapy, consists of gold-induced autologous conditioned serum (GOLDIC®). Gold compounds (aurothiomalate) inhibit the production of nitric oxide (NO) of chondrocytes. Nitric oxide mediates the destructive effects of IL-1 and TNF (*Green* et al. 2006), which include reduced collagen and proteoglycan production, apoptosis of chondrocytes and stimulation of metalloproteases (*Vuolteenaho* et al. 2005). GOLDIC® in vitro studies showed that it not only inhibits catabolic factors, but increases anti-catabolic and anabolic factors. Amongst other things, it could be proved that Gelsolin, key-protein in cell-metabolism, is increased significantly (*Schneider* 2011). In a large uncontrolled case study that constituted the first report of the clinical application of the GOLDIC® technique, the treatment of horses with different grades of joint disease and lameness resulted in marked improvement in clinical signs (*Schneider* and *Veith* 2013). However, the purpose of that study was merely to screen the usefulness of GOLDIC® for the treatment of arthrogenic lameness in horses.

The purpose of the present study was to compare the efficacy of the GOLDIC® treatment with that of corticosteroids and hyaluronic acid in horses with osteoarthritis. The hypothesis was that both treatments have a therapeutic effect but that the effect of the GOLDIC® treatment is greater.

Material and methods

This clinical study was designed as a prospective randomized controlled lameness trial: The study included horses that were admitted to the Equine Clinic at the Vetsuisse Faculty of the University of Zurich and to the private equine clinic "Fohlenweide" (Heigenkam, Germany) because of lameness attributable to arthropathy. The criteria for inclusion into the study were as follows: the lameness had been present for a minimum of three weeks, the lameness was caused by joint disease diagnosed using nerve blocks and if possible imaging modalities and systemic or intra-articular treatments had not been carried out in the previous three weeks. Horses with conditions amenable to surgical treatment (e.g. osteochondritis) were excluded. After history taking, the horses underwent clinical and orthopaedic examinations. Thirty horses fulfilled the criteria for inclusion into this study, 16 of which were treated with the GOLDIC® method and 14 with betamethasone and hyaluronic acid. The mean age was 12.2 years (range 4 to 18 years) in group A and 10.7 years (2 to 18 years) in group B. The signalment of the horses, the history, the joint affected and adverse effects of treatment are shown in Table 1. Lameness was assessed using the AAEP *Grading* system (AAEP 2019). The results of the flexion test and the degree of joint effusion were classified as 0 (negative), 1 (mild), 2 (moderate) and 3 (severe). At the end of treatment, the degree of improvement of lameness was assessed.

The different groups were randomized on the basis of a computer-generated list: Group A (Hyaluronic acid/steroid) and Group B (GOLDIC®).

Group A: Horses in this group were given a single intra-articular injection of 12–18 mg betamethasone acetate[a] and 20 mg hyaluronic acid[b]. The injection site was prepared aseptically, and depending on the temperament of the horse, xylazine[c] (0.5 mg/kg) and butorphanol[d] (0.02 mg/kg) were given for sedation.

Group B: Horses in this group received 4 ml GOLDIC®[e] activated serum once per week for four weeks using the same injection technique as in group A. The horses underwent clinical examination before each injection, and the degree of joint effusion, swelling and other abnormalities were recorded.

Preparation of GOLDIC®

The gold-induced, autologous-conditioned serum was produced in accordance to the manufacturer's guidelines (Arthrogen GmbH). The first injection was performed on day 1 after serum incubation; the other three serum aliquots were stored at –20 °C until the designated day of injection.

Aftercare

After each joint injection, the horses were confined to a box stall for two days, after which time they were hand walked for

Table 1 Codes of the study horses, sex, age, diagnosis, localisation of the arthrogenic lameness, duration of lameness and clinical evaluations of the treated horses. Group A was treated with a single corticosteroid and hyaluronic acid injection, group B with GOLDIC® injections. | *Codes der Versuchspferde, Geschlecht, Alter, Diagnose, Lokalisation der arthrogenen Lahmheit, Dauer der Lahmheit und klinische Bewertungen der behandelten Pferde. Gruppe A wurde mit einer einzigen Kortikosteroid- und Hyaluronsäure-Injektion behandelt, Gruppe B mit GOLDIC®-Injektionen.*

Group	Age (y)	Sex	Diagnosis	Localisation	Duration	Joint Anesthesia	Return to Function	Adverse Events
A	3	f	Sclerosis third carpal bone	carpal joint front left	weeks	positive	yes	no
A	18	f	hgr OA	tarosmetatarsal joint right	months	positive		no
A	11	m	lgr OA	carpal and carpo-metacarpal joint left	months	positive	no	no
A	7	m	no OA	stifle joint	weeks	positive	no	no
A	10	m	no Rx	tarosmetatarsal joint	weeks	positive	yes	no
A	17	m	mgr OA	fetlock joint left forelimb	weeks	positive	yes	no
A	5	f	no Rx	fetlock joint left forelimb	weeks	positive	yes	no
A	2	m	no Rx	stifle joint	weeks	-	yes	no
A	16	f	lgr OA	pastern joint hind leg right	weeks	positive	?	joint flare after anesthesia
A	17	m	lgr-mgr OA	coffin joint both forlimbs	months	positive	no	no
A	3	f	mgr OA	carpal joint right forelimb	weeks	-	yes	no
A	16	f	lgr OA	fetlock joint right forelimb	months	-	no	no
A	18	m	hgr OA	talocalcanean joint	weeks	positive	no	no
A	8	f	mgr OA	antebrachiocarpal joint left	weeks	positive		joint flare after anesthesia
B	11	m	cyst femoral condyle	stifle joint	months	positive	no	no
B	18	f	mgr OA	fetlock joint left forelimb	months	-	yes	no
B	12	m	mgr OA	Scapulohumeral joint	months	-	no	no
B	17	f	no OA	coffin joint right forelimb	months	positive	no	increase of lameness for 24 h
B	4	f	no Rx	carpal joint left forelimb	weeks	positive	yes	increased swelling after the first injection
B	8	f	lgr OA	coffin joints both forelimbs	weeks	positive	yes	no
B	5	f	mgr -hgr OA	carpal joint right forelimb	weeks	-		no
B	16	m	mgr OA	coffin joint left forelimb	weeks	positive	yes	no
B	17	m	hgr OA	coffin joint right forelimb	weeks	positive	yes	no
B	18	m	mgr OA	hock right side	months	positive	yes	no
B	6	m	mgr OA	MCG right	months	positive	yes	no
B	10	m	mgr -hgr OA	coffin joint left forelimb	weeks	positive	yes	no
B	18	m	mgr OA	carpal joint right forelimb	months	positive	yes	no
B	10	m	mgr -hgr OA	coffin joint both forelimbs	months	positive	yes	no
B	13	m	mgr OA	coffin joint right side	months	positive	yes	no
B	13	f	mgr -hgr OA	coffin joint right side	months	positive	yes	increased swelling after the second injection

(hgr OA = high grade osteoarthritis; mgr OA = mid grade osteoarthritis, lgr OA = low grade osteoarthritis; Rx = x-ray) | *(hgr OA = hochgradige Osteoarthritis; mgr OA = mittelgradige Osteoarthritis; lgr OA = leichtgradige Osteoarthritis; x = Röntgenaufnahme)*

the entire duration of the treatment. At the end of the treatment period, exercise was gradually increased depending on the degree of lameness.

Outcome

The main endpoint was the degree of lameness assessed using the AAEP *Grading* system 3, 6, 12 and 36 months after treatment. Further endpoints were the recovery to the point of full function of the leg, and radiographic findings (osteoarthrosis progression).

Power analysis

The number of patients required to detect an effect of the GOLDIC® method was determined based on a previous pilot study (*Schneider* and *Veith* 2013). The AAEP lameness grade was the primary endpoint and a decrease in lameness by one grade was considered clinically significant. A sample size of 28 patients was required for 80 % power ($\alpha = 0.05$, standard deviation = 1.3) to reject the null hypothesis that both treatments were equal. Therefore, 30 horses were used in the present study.

Statistical analysis

The program Sigma Stat 3.5 was used for statistical calculations. To determine how closely the data fits a normal distribution, we computed a Kolmogorov-Smirnov Goodness of Fit test. The data could not be assumed to be reasonably normally distributed. For further analyzes we used non-parametric statistical tests. For tests within each group (HA+S and GOLDIC®) we used Friedman's Two Way ANOVA of Ranks and Wilcoxon signed Rank Test. For tests between the groups (HA+S and GOLDIC®) we used Mann-Whitney U Test. As Mann-Whitney U Tests between T0 values of both groups (HA+S and GOLDIC®) showed that the two samples are not distributed identically, it was not usefull to compare the T1, T2, T3, T4 values directly between the two groups (HA+S and GOLDIC®). We defined DELTA values for T1-T4 as the difference relative to T0 using Mann-Whitney U Test.

Results

All horses showed a marked improvement in their degree of lameness by time. The AAEP scores of all horses are demonstrated in Figure 1.

Both treatment groups have a positive temporal development of the AAEP-Score. Comparison of the different times within each group shows higher differences with lower probabilities for same distribution in group B (GOLDIC®). Also, the DELTA Values are higher in group B (GOLDIC®).

In Figure 1, AAEP-Score Means showed clearly that in group A (HA+S) we have a nearly linear temporal development of the AAEP-Score over all Times T0-T4. In group B (GOLDIC®) we found a much stronger but also nearly linear improvement of the AAEP-Score over T0-T2. Looking at T0-T4 it seems that we have an asymptotic approach to a minimum value after T2.

In the GOLDIC® group 13 of 16 horses got back to their original performance level while three horses were competing at a lower level than before. In this group, we had 2 drop outs at 12 months. One horse could not be followed after being sold to a new owner. The other horse was euthanized based on the cyst in the treated joint.

On the other side, the control group had 6 horses out of 14, which went back to their original state of performance while five weren't capable of getting back. We had one lost of follow-up after 3 and 6 months based on another disease and 2 further drop-outs after 3 years (the owner of these two horses could not be reached for documentation).

The GOLDIC® group had two horses with radiological progression, but they were still capable of being used in their full and original activity. In both groups, no severe side effects could be seen. Nevertheless, one horse got worse for about one grade for a few days while treatment was done.

The age, sex, radiological morphology and duration of lameness had no effect on the results of treatment.

Discussion

This is the first study of the efficacy of the injections of gold-induced, autologous conditioned serum (GOLDIC®) for the treatment of arthrogenic lameness in horses in a prospective comparative study. Intra-articular injections of a corticosteroid and hyaluronic acid, which is commonly used and well established in veterinary medicine, was used in the control group. Corticosteroids have been used for decades for this purpose and are considered a standard treatment for arthrogenic lameness in veterinary medicine (*Frean* et al. 2002, *Schaefer* et al. 2009, *Trotter* 1996). However, treatment with corticosteroids is strictly symptomatic because it does not affect the aetiology of the disease process. A major drawback is the introduction of crystalline steroidal elements into the joint. Repeated intra-articular injections of corticosteroids can cause irritation of the intra-articular structures because of aggrega-

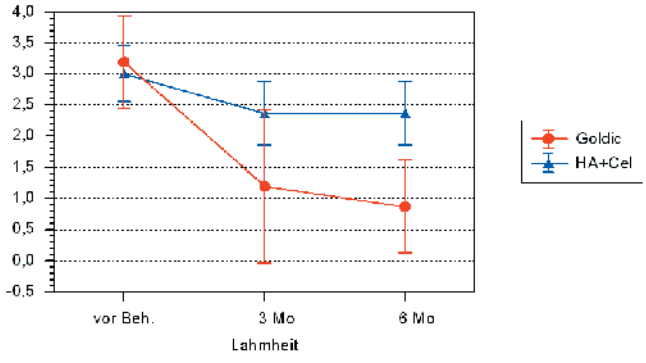

Fig. 1 AAEP lameness scores of all horses in groups A (blue line) and B (red line) before treatment and at follow-up examinations. | *AAEP-Lahmheitsbewertungen aller Pferde in den Gruppen A (blaue Säulen) und B (rote Säulen) vor der Behandlung und bei Folgeuntersuchungen.*

tion of these crystals (*Jones* and *Doherty* 1996, *Friedman* and *Moore* 1980, *Gaffney* et al. 1995).

The treatment of arthrosis with hyaluronic acid is controversial in human medicine (*Caborn* et al. 2004, *Day* et al. 2004, *Lee* et al. 2006, *Lundsgaard* et al. 2008, *Raman* et al. 2008, *Raynauld* et al. 2003, *Huang* et al. 2011, *Juni* et al. 2007, *Puhl* et al. 1993, *Qvist* et al. 2008, *Maheu* et al. 2011). Although many studies have investigated this drug a positive effect on damaged joint cartilage has not been demonstrated (*Rutjes* et al. 2012). Recently, the American Academy of Orthopedic Surgeons published a retraction of a recommendation for the treatment of knee osteoarthritis with hyaluronic acid products based on a meta-analysis (*Jevsevar* et al. 2013) but hyaluronic acid continues to be used by physicians.

Several novel treatments based on biological processes rather than providing mere pain control have recently been introduced, but the demonstration of efficacy has been difficult (*Broeckx* et al. 2019). The use of the interleukin-1 receptor antagonist protein (IRAP®), cell-based procedures such as platelet-rich plasma (PRP) and the transplantation of mesenchymal stem-cells have not proven useful for the treatment of degenerative joint disease in horses (*Bertone* et al. 2014, *Ehrle* et al. 2013, *Fahie* et al. 2013, *Franklin* and *Cook* 2013). In the daily use, they are often viewed critically (*Hildner* et al. 2011).

We designed a prospective and controlled study to investigate the effect of the GOLDIC® method for the treatment of arthrogenic lameness in horses with the final follow-up examination at 3 years. This was done to critically examine long-term effects of the treatments. The follow-up period was longer than in other studies that investigated the treatment of arthrogenic lameness.

Both treatments tested in this study led to a decrease in lameness but the effect of the GOLDIC® technique was greater and statistically significant. Only the horses treated with the GOLDIC® method had significantly lower lameness grades 3 years after treatment than before treatment. The results of the present study are in agreement with another study that also documented significant long-lasting benefits of the GOLDIC® method in the treatment of arthrogenic lameness in horses (*Schneider* 2011, *Schneider* et al. 2017).

The mode of action of the GOLDIC® procedure is not well understood. Nevertheless, GOLDIC® has shown in in-vitro studies that plasma Gelsolin could be elevated in the autologous serum significantly (*Schneider* et al. 2017). Gelsolin is an actin-binding protein and occurs in cells (cytoskeleton) and in plasma (*Silacci* et al. 2004). The cytoskeleton is responsible for the viscoelasticity of this cells (*Trickey* et al. 2004). Furthermore, important functions of cells are regulated by Gelsolin: Cell motility, phagocytosis, apoptosis and the activation of thrombocytes (*Silacci* et al. 2004). The concentration of Gelsolin in plasma is decreased according to different tissue degenerating diseases (*Suhler* et al. 1997). Experiments have shown decreased plasma Gelsolin concentrations in animals with sepsis, and treatment with Gelsolin had a positive effect on the survival rate in these animals (*Lee* et al. 2007). Plasma Gelsolin serves as a buffer to intercept inflammatory reactions of the body (*DiNubile* 2008) and was found to be decreased in rheumatic arthritis (*Osborn* et al. 2008).

It was beyond the scope of this study to collect serum and synovial fluid samples for measurements of Gelsolin in response to the GOLDIC® treatment. A clinical study of human osteoarthritis in knee joints showed that intra-articular

Table 2 AAEP lameness in groups A and B before treatment and at follow-up examinations (Median values including 25th and 75th percentiles and lost of follow-up | *AAEP-Lahmheit in den Gruppen A und B vor der Behandlung und bei Nachuntersuchungen (Medianwerte einschließlich 25. und 75. Perzentil und Verluste bei Nachuntersuchungen*

Group	N	Missing	Median	25%	75%
Goldic pre	16	0	2'000	2'000	3'000
HA+S pre	14	0	3'000	3'000	3'000
Goldic 3mo	16	0	2'000	1'000	2'000
HA+S 3mo	13	1	3'000	2'250	3'000
Goldic 6mo	16	0	1'000	0.000	1'000
HA+S 6mo	13	1	2'000	2'000	3'000
Goldic 12 mo	16	2	0.500	0.000	1'000
HA+S 12mo	13	2	2'000	2'000	2'000
Goldic 3y	16	2	1'000	0.000	1'000
HA+S 3y	12	4	2'000	1'000	2'000

HA+S = Hyaluronic acid and steroids)/ *HA+S = Hyaluronsäure und Steroide*

Table 3 Statistical analysis of the AAEP lameness grades score at different follow-up examinations demonstrated by differences of ranks, Q values and P values. | *Die statistische Analyse der AAEP-Lahmheitsgrade ergab bei den verschiedenen Folgeuntersuchungen Unterschiede in den Rängen, Q-Werten und P-Werten*

Comparison	Diff. of Ranks	Q	P	P < 0.050
Goldic pre vs Goldic > 3 y	62'955	4'464	<0.001	Yes
Goldic pre vs Goldic > 6 mo	62'277	4'416	<0.001	Yes
Goldic pre vs Goldic 3–6	56'531	4'149	0.002	Yes
HA+S < 3mo vs Goldic > 3 y	76'268	5'031	<0.001	Yes
HA+S < 3mo vs Goldic > 6 mo	75'589	4'986	<0.001	Yes
HA+S < 3mo vs Goldic 3–6	69'844	4'746	<0.001	Yes
HA+S 3–6 vs Goldic > 3 y	63'101	4'162	0.001	Yes
HA+S 3–6 vs Goldic > 6 mo	62'423	4'117	0.002	Yes
HA+S 3–6 vs Goldic 3–6	56'677	3'851	0.005	Yes
HA+S pre vs Goldic < 3mo	48'214	3'419	0.028	Yes
HA+S pre vs Goldic > 3 y	81'857	5'620	<0.001	Yes
HA+S pre vs Goldic > 6 mo	81'179	5'573	<0.001	Yes
HA+S pre vs Goldic 3–6	75'433	5'349	<0.001	Yes
HA+S < 3mo vs Goldic < 3mo	42'625	2'896	0.170	No
HA+S > 6 vs Goldic > 3 y	50'597	3'259	0.050	No
HA+S pre vs HA+S > 3 y	43'589	2'552	0.482	No

treatment with gold-activated serum (GOLDIC®) resulted in a significant increase of Gelsolin in synovial fluid (*Schneider* 2011).

One limitation of this study was the low number of cases and the heterogeneity of joints affected. Still, in this study, the intra-articular treatment of arthrogenic lameness in horses with the GOLDIC® method yielded significantly better short- and long-term results than the traditional treatment with corticosteroids and hyaluronic acid. Further studies are needed to substantiate whether the beneficial effect of the GOLDIC® method is attributable to an increase in the actin-binding protein, Gelsolin, in synovial fluid.

Manufacturer's addresses

[a] Celestone-Chronodose®, Essex Chemie, Switzerland
[b] SynovaMed AG, Liechtenstein
[c] Xylazin® Streuli Pharma Switzerland
[d] Alvegesic® 10%, Virbac Switzerland
[e] Arthrogen med vet GmbH, Germany

Animal welfare statement

This study was approved by the veterinary office of the Canton of Zurich (4312/9.3.2010).

Conflict of interest

The authors declare that they have no conflict of interest. *Anton Fürst* is member of the Medical board of Arthrogen GmbH but does not have any financial benefits based on this membership.

References

American Association of Equine Practitioners AAEP (2019) Evaluating the lame horse. https://aaep.org/horsehealth/lameness-exams-evaluating-lame-horse

Baltzer A. W., Drever R., Granrath M., Godde G., Klein W., Wehling P. (2003) Intraartikuläre Therapie der Gonarthrose mit autologem Interleukin-1 Rezeptor Antagonisten (IL-1Ra). Dtsch. Z. Sportmed. 54, 209–211

Baltzer A. W., Moser C., Jansen S. A., Krauspe R. (2009) Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthitis Cartil. 17, 152–160; DOI 10.1016/j.joca.2008.06.014

Bertone A. L., Ishihara A., Zekas L. J., Welllman M. L., Lewis K. B., Schwarze R. A., Barnaba A. R., Schmall M. L., Kanter P. M., Genovese R. L. (2014) Evaluation of a single intra-articular injection of autologous protein solution for treatment of osteoarthritis in horses. Am. J. Vet. Res. 75, 141–151; DOI 10.2460/ajvr.75.2.141

Bertone A. L., Palmer J. L., Jones J. (2001) Synovial fluid cytokines and eicosanoids as markers of joint disease in horses. Vet. Surg. 30, 528–538; DOI 10.2460/ajvr.75.2.141

Bondeson J., Wainwright S. D., Lauder S., Amos N., Hughes C. E. (2006) The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis. Arthritis Res. Ther. 8, R187; DOI 10.1186/ar2099

Bresnihan B., Alvaro-Gracia J. M., Cobby M., Doherty M., Domljan Z., Emery P., Nuki G., Pavelka K., Rau R., Rozman B., Watt I., Williams B., Aitchison R., McCabe D., Musikic P. (1998) Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum. 41, 2196–2204; DOI 10.1002/15290131(199812)41:12 < 2196::AID-ART15 > 3.0.CO;2-2

Broeckx S. Y., Martens A. M., Bertone A. L., Van Brantegem L., Duchateau L., Van Hecke L., Dumoulin M., Oosterlinck M., Chiers, K., Hussein H., Pille F., Spaas J. H. (2019) The use of equine chondrogenic-induced mesenchymal stem cells as a treatment for osteoarthritis: A randomised, double-blinded, placebo-controlled proof-of-concept study. Equine Vet. J. 51, 878–794; DOI 10.1111/evj.13089

Buckwalter J. A. (1995) Osteoarthritis and articular cartilage use, disuse, and abuse: experimental studies. J. Rheumatol. Suppl 43, 13–15

Buckwalter J. A. (2003) Sports, joint injury, and posttraumatic osteoarthritis. J. Orthop. Sports Phys. Ther. 33, 578–588; DOI 10.2519/jospt.2003.33.10.578

Buckwalter J. A., Brown T. D. (2004) Joint injury, repair, and remodeling: roles in post-traumatic osteoarthritis. Clin. Orthop. Relat. Res. 423, 7–16

Caborn D., Rush J., Lanzer W., Parenti D., Murray C., Synvisc 901 Study Group (2004) A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. J. Rheumatol. 31, 333–343

Caron J. P. (2005) Intra-articular injections for joint disease in horses. Vet. Clin. North Am. Equine Pract. 21, 559–573; DOI 10.1016/j.cveq.2005.07.003

Clegg P. D., Burke R. M., Coughlan A. R., Riggs C. M., Carter S. D. (1997a) Characterisation of equine matrix metalloproteinase 2 and 9; and identification of the cellular sources of these enzymes in joints. Equine Vet. J. 29a, 335–342; DOI 10.1111/j.2042-3306.1997.tb03136.x

Clegg P. D., Coughlan A. R., Riggs C. M., Carter S. D. (1997b) Matrix metalloproteinases 2 and 9 in equine synovial fluids. Equine Vet. J. 29b, 343–348; DOI 10.1111/j.20423306.1997.tb03137.x

Cruz A. M., *Hurtig* M. B. (2008) Multiple pathways to osteoarthritis and articular fractures: is subchondral bone the culprit? Vet. Clin. North Am. Equine Pract. 24, 101–116; DOI 10.1016/j.cveq.2007.12.001

David F., Farley J., Huang H., Lavoie J. P., Laverty S. (2007) Cytokine and chemokine gene expression of IL-1beta stimulated equine articular chondrocytes. Vet. Surg. 36, 221–227; DOI 10.1111/j.1532-950X.2007.00253.x

Day R., Brooks P., Conaghan P. G., Petersen M. (2004) A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. J. Rheumatol. 3, 775–782

DiNubile M. J. (2008) Plasma gelsolin as a biomarker of inflammation. Arthritis Res. Ther. 10, 124; DOI 10.1186/ar2547

Ehrle A., Fürst A., Lischer C. J. (2013) Regenerative and innovative joint medication in the horse – Part 2: Efficacy and adverse effects of joint medication in the horse – A review of the literature. Pferdeheilkunde 29, 212–218; DOI 10.21836/PEM20130208

Fahie M. A., Ortolano G. A., Guercio V., Schaffer J. A., Johnston G., Au J., Hettlich B. A., Phillips T., Allen M. J., Bertone A. L. (2013) A randomized controlled trial of the efficacy of autologous platelet therapy for the treatment of osteoarthritis in dogs. J. Am. Vet. Med. Assoc. 243, 1291–1297; DOI 10.2460/javma.243.9.1291

Fortier L. A. (2005) Systemic therapies for joint disease in horses. Vet. Clin. North Am. Equine Pract. 21, 547–557; DOI 10.1016/j.cveq.2005.07.002

Franklin S. P., Cook J. L. (2013) Prospective trial of autologous conditioned plasma versus hyaluronan plus corticosteroid for elbow osteoarthritis in dogs. Can. Vet. J. 54, 881–884

Frean S. P., Cambridge H., Lees P. (2002) Effects of anti-arthritic drugs on proteoglycan synthesis by equine cartilage. J. Vet. Pharmacol. Ther. 25, 289–298

Friedman D. M., Moore M. E. (1980) The efficacy of intraarticular steroids in osteoarthritis: a double-blind study. J. Rheumatol. 7, 850–856

Frisbie D. D., Kawcak C. E., McIlwraith C. W., Werpy N. M. (2009) Evaluation of polysulfated glycosaminoglycan or sodium hyaluronan administered intra-articularly for treatment of horses with experimentally induced osteoarthritis. Am. J. Vet. Res. 70, 203–209; DOI 10.2460/ajvr.70.2.203

Frisbie D. D., Kawcak C. E., Werpy N. M., Park R. D., McIlwraith C. W. (2007) Clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum in horses with experimentally induced osteoarthritis. Am. J. Vet. Res. 68, 290–296; DOI 10.2460/ajvr.68.3.290

Gaffney K., Ledingham J., Perry J. D. (1995) Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response. Ann. Rheum. Dis. 54, 379–381; DOI 10.1136/ard.54.5.379

Goldring M. B., Birkhead J., Sandell L. J., Kimura T., Krane S. M. (1988) Interleukin 1 suppresses expression of cartilage-specific types II and IX collagens and increases types I and III collagens in human chondrocytes. J. Clin. Invest. 82, 2026–2037; DOI 10.1172/JCI113823

Green D. M., Noble P. C., Ahuero J. S., Birdsall H. H. (2006) Cellular events leading to chondrocyte death after cartilage impact injury. Arthritis Rheum. 54, 1509–1517; DOI 10.1002/art.21812

Guilak F., Fermor B., Keefe F. J., Kraus V. B., Olson S. A., Pisetsky D. S., Setton L. A., Weinberg J. B. (2004) The role of biomechanics and inflammation in cartilage injury and repair. Clin. Orthop. Relat. Res. 423, 17–26; DOI 10.1097/01.blo.0000131233.83640.91

Hildner F., Albrecht C., Gabriel C., Redl H., van Griensven M. (2011) State of the art and future perspectives of articular cartilage regeneration: a focus on adipose-derived stem cells and platelet-derived products. J. Tissue Eng. Regen. Med. 5, 36–51; DOI 10.1002/term.386

Huang T. L., Chang C. C., Lee C. H., Chen S. C., Lai C. H., Tsai C. L. (2011) Intra-articular injections of sodium hyaluronate (Hyalgan®) in osteoarthritis of the knee. a randomized, controlled, double-blind, multicenter trial in the asian population. BMC Musculoskelet. Disord. 12, 221; DOI 10.1186/1471-2474-12-221

Jaeger G. T., Larsen S., Søli N., Moe L. (2006) Double-blind, placebo-controlled trial of the pain-relieving effects of the implantation of gold beads into dogs with hip dysplasia. Vet. Rec. 158 , 722–726 ; DOI 10.1136/vr.158.21.722

Janssen I., Koene M., Lischer C. J. (2012) Intraarticular application of polyacrylamide hydrogel as a treatment of osteoarthritis in the distal interphalangeal joint: case series with 12 horses. Pferdeheilkunde 28, 650–656; DOI 10.21836/PEM20120602

Jevsevar D. S, Brown G. A., Jones D. L., Matzkin E. G., Manner P. A., Mooar P., Schousboe J. T., Stovitz S., Sanders J. O., Bozic K. J., Goldberg M. J., Martin W. R. 3rd, Cummins D. S., Donnelly P., Woznica A., Gross L., American Academy of Orthopaedic Surgeons (2013) The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition. J. Bone Joint Surg. Am. 95, 1885–1886; DOI 10.2106/00004623-201310160-00010

Johnston S. A. (1997) Osteoarthritis. Joint anatomy, physiology, and pathobiology. Vet. Clin. North Am. Small Anim. Pract 27, 699–723; DOI 10.1016/S0195-5616 (97)50076-3

Jones A., Doherty M. (1996) Intra-articular corticosteroids are effective in osteoarthritis but there are no clinical predictors of response. Ann. Rheum. Dis. 55, 829–832; DOI 10.1136/ard.55.11.829

Juni P., Reichenbach S., Trelle S., Tschannen B., Wandel S., Jordi B., Züllig M., Guetg R., Häuselmann H. J., Schwarz H., Theiler R., Ziswiler H. R., Dieppe P. A., Villiger P. M., Egger M., Swiss Viscosupplementation Trial Group (2007) Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial. Arthritis Rheum. 56, 3610–3619; DOI 10.1002/art.23026

Kobayashi M., Squires G. R., Mousa A., Tanzer M., Zukor D. J., Antoniou J., Feige U., Poole A. R. (2005) Role of interleukin-1 and tumor necrosis factor alpha in matrix degradation of human osteoarthritic cartilage. Arthritis Rheum. 52, 128–135; DOI 10.1002/art.20776

Lawrence R. C., Helmick C. G., Arnett F. C., Deyo R. A., Felson D. T., Giannini E. H., Heyse S. P., Hirsch R., Hochberg M. C., Hunder G. G., Liang M. H., Pillemer S. R., Steen V. D., Wolfe F. (1998) Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum. 41, 778–799;DOI 10.1002/1529-0131 (199805)41:5 < 778::AID-ART4 > 3.0.CO;2-V

Lee P. B., Kim Y. C., Lim Y. J., Lee C. J, Sim W. S., Ha C. W., Bin S. I., Lim K. B., Choi S. S., Lee S. C. (2006) Comparison between high and low molecular weight hyaluronates in knee osteoarthritis patients: open-label, randomized, multicentre clinical trial. J. Int. Med. Res. 34, 77–87; DOI 10.1177/14732300603400110

Lee P. S., Waxman A. B., Cotich K. L., Chung S. W., Perrella M. A., Stossel T. P. (2007) Plasma gelsolin is a marker and therapeutic agent in animal sepsis. Crit. Care Med. 35, 849–855; DOI 10.1097/01.CCM.0000253815.26311.24

Loeser R. F. (2006) Molecular mechanisms of cartilage destruction: mechanics, inflammatory mediators, and aging collide. Arthritis Rheum. 54, 1357–1360; DOI 10.1002/art.21813

Lukoschek M., Boyd R. D., Schaffler M. B., Burr D. B., Radin E. L. (1986) Comparison of joint degeneration models. Surgical instability and repetitive impulsive loading. Acta Orthop. Scand. 57, 349–353; DOI 10.3109/17453678608994409

Lundsgaard C., Dufour N., Fallentin E., Winkel P., Gluud C. (2008) Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: a randomized clinical trial. Scand. J. Rheumatol. 37, 142–150; DOI 10.1080/03009740701813103

Maheu E., Zaim M., Appelboom T., Jeka S., Trc T., Berenbaum F., Maasalu K., Berenbaum F. (2011) Comparative efficacy and safety of two different molecular weight (MW) hyaluronans F60027 and Hylan G-F20 in symptomatic osteoarthritis of the knee (KOA). Results of a non inferiority, prospective, randomized, controlled trial. Clin. Exp. Rheumatol. 29, 527–535

McIlwraith C. W. (1996) General Pathobiology of the Joint and Response to Injury. In: *McIlwraith* C.W. and *Trotter* G.W., editors. Joint Disease in the Horse, 1st edn. Saunders, Philadelphia, pp 40–70

Meijer H., Reinecke J., Becker C., Tholen G., Wehling P. (2003) The production of anti-inflammatory cytokines in whole blood by physico-chemical induction. Inflamm. Res. 52, 404–407; DOI 10.1007/s00011-003-1197-1

Norrdin R. W., Kawcak C. E., Capwell B. A., McIlwraith C. W. (1989) Subchondral bone failure in an equine model of overload arthrosis. Bone 22, 133–139; DOI 10.1016/S8756-3282 (97)00253-6

Osborn T. M., Verdrengh M., Stossel T. P., Tarkowski A., Bokarewa M. (2008) Decreased levels of the gelsolin plasma isoform in patients with rheumatoid arthritis. Arthritis Res. Ther. 10, R117; DOI 10.1186/ar2520

Pelletier J. P., Martel-Pelletier J., Abramson S. B. (2001) Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum. 44, 1237–1247; DOI 10.1002/1529-0131 (200106)44:6 < 1237::AID-ART214 > 3.0.CO;2-F

Pool R. R., Meagher D. M. (1990) Pathologic findings and pathogenesis of racetrack injuries. Vet. Clin. North Am. Equine Pract. 6, 1–30; DOI 10.1016/S0749-0739 (17)30555-2

Puhl W., Bernau A., Greiling H., Köpcke W., Pförringer W., Steck K. J., Zacher J., Scharf H. P. (1993) Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. Osteoarthritis Cartil. 1, 233–241; DOI 10.1016/S1063-4584 (05)80329-2

Qvist P., Bay-Jensen A. C., Christiansen C., Dam E. B., Pastoureau P., Karsdal M. A. (2008) The disease modifying osteoarthritis drug (DMOAD): Is it in the horizon? Pharmacol. Res. 58, 1–7; DOI 10.1016/j.phrs.2008.06.001

Radin E. L., Rose R. M. (1986) Role of subchondral bone in the initiation and progression of cartilage damage. Clin. Orthop. Relat. Res. 213, 34–40; DOI 10.1097/00003086-198612000-00005

Raman R., Dutta A., Day N., Sharma H. K., Shaw C. J., Johnson G. V. (2008) Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of osteoarthritis of the knee - a prospective randomized clinical trial. Knee 15, 318–324; DOI 10.1016/j.knee.2008.02.012

Raynauld J. P., Buckland-Wright C., Ward R., Choquette D., Haraoui B., Martel-*Pelletier* J., Uthman I., Khy V., Tremblay J. L., Bertrand C., *Pelletier* J. P. (2003) Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo- controlled trial. Arthritis Rheum. 48, 370–377; DOI 10.1002/art.10777

Rossdale P. D., Hopes R., Digby N. J., Offord K. (1985) Epidemiological study of wastage among racehorses 1982 and 1983. Vet. Rec. 116, 66–69; DOI 10.1136/vr.116.3.66

Rutjes A. W., Jüni P., da Costa B. R., Trelle S., Nüesch E., Reichenbach S. (2012) Viscosupplementation for osteoarthritis of the knee: a systematic review and Meta-analysis. Ann. Intern. Med. 157, 180–191; DOI 10.7326/0003-4819-157-3-201208070-00473

Samuels J., Krasnokutsky S., Abramson S. B. (2008) Osteoarthritis: a tale of three tissues. Bull. NYU Hosp. Joint Dis. 66, 244–250

Schaefer E. C., Stewart A. A., Durgam S. S., Byron C. R., Stewart M. C. (2009) Effects of sodium hyaluronate and triamcinolone acetonide on glucosaminoglycan metabolism in equine articular chondrocytes treated with interleukin-1. Am. J. Vet. Res. 70, 1494–1501; DOI 10.2460/ajvr.70.12.1494

Schneider U. (2011) International Patent Application No. PCT/DE2011/001322

Schneider U., Veith G. (2013) First Results on the Outcome of Gold-induced, Autologous-conditioned Serum (GOLDIC) in the Treatment of Different Lameness-associated Equine Diseases. J. Cell Sci. Ther. 5, 151; DOI 10.4172/2157-7013.1000151

Schneider U., Wallich R., Felmet G., Murrell W. D. (2017) Gold-Induced Autologous Cytokine Treatment in Achilles Tendinopathy. In: G.L. Canata et al. (eds.) Muscle Tendon Injuries, ISAKOS. 411–420; DOI 10.1007/978-3-662-54184-5_39

Silacci P., Mazzolai L., Gauci C., Stergiopulos N., Yin H. L., Hayoz D. (2004) Gelsolin superfamily proteins: key regulators of cellular functions. Cell Mol. Life Sci. 61, 2614–2623; DOI 10.1007/s00018-004-4225-6

Simmons E. J., Bertone A. L., Weisbrode S. E. (1999) Instability-induced osteoarthritis in the metacarpophalangeal joint of horses. Am. J. Vet. Res. 60, 7–13

Spiers S., May S. A., Bennett D., Edwards G. B. (1994) Cellular sources of proteolytic enzymes in equine joints. Equine Vet. J. 26, 43–47; DOI 10.1111/j.2042-3306.1994.tb04329.x

Suhler E., Lin W., Yin H. L., Lee W. M. (1997) Decreased plasma gelsolin concentrations in acute liver failure, myocardial infarction, septic shock, and myonecrosis. Crit. Care Med. 25, 594–598; DOI 10.1097/00003246-199704000-00007

Trickey W. R., Vail T. P., Guilak F. (2004) The role of the cytoskeleton in the viscoelastic properties of human articular chondrocytes. J. Orthop. Res. 22, 131–139; DOI 10.1016/S0736-0266 (03)00150-5

Trotter G. W. (1996) Intraarticular Corticosteroids. In: *McIlwraith* C. W., *Trotter* G. W., editors. Joint Disease in Horses, 1st edn., Saunders, Philadelphia. pp. 237–256

von Rechenberg B., McIlwraith C. W., Akens M. K., Frisbie D. D., Leutenegger C., Auer J. A. (2000) Spontaneous production of nitric oxide (NO), prostaglandin (PGE2) and neutral metalloproteinases (NMPs) in media of explant cultures of equine synovial membrane and articular cartilage from normal and osteoarthritic joints. Equine Vet. J. 32, 140–150; DOI 10.2746/042516400777591598

Vuolteenaho K., Kujala P., Moilanen T., Moilanen E. (2005) Aurothiomalate and hydroxychloroquine inhibit nitric oxide production in chondrocytes and in human osteoarthritic cartilage. Scand. J. Rheumatol. 34, 475–479; DOI 10.1080/03009740510026797

Warner K., Schulze T., Lischer C. J. (2016) Treatment of Osteoarthritis with ACS (IRAP®) on 26 horses – retrospective study. Pferdeheilkunde 32, 241–248; DOI 10.21836/PEM20160307

Young B. D., Samii V. F., Mattoon J. S., Weisbrode S. E., Bertone A. L. (2007) Subchondral bone density and cartilage degeneration patterns in osteoarthritic metacarpal condyles of horses. Am J Vet Res 68, 841–849, DOI: 10.2460/ajvr.68.8.841