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Research Article

Clinical Efficacy of Intra-Articular Injections of Autologous Conditioned Serum Compared with Dexamethasone for The Treatment of Bilateral Knee Osteoarthritis. A Retrospective Analysis

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Abstract

Objective: Comparison of two effective intra-articular injection therapies, autologous conditioned serum versus dexamethasone in patients with chronic bilateral knee osteoarthritis.

Methods: In a monocentric closed cohort study with relocated baseline and an internal intra-individual matched comparison of the left and right knee, 34 patients (n = 68 knees) with knee osteoarthritis grade I-III were included in the analysis. Clinical scores were analyzed before intra-articular injection and at control visits. All patients received a series of six 2mL intra-articular injections with ACS into one knee over three weeks. All patients received one 5mg Dexamethasone injection in the contralateral knee. Both treatments are clinical routine and efficacious. Efficacy for each knee was measured by NRS pain score, WOMAC index and GPA questionnaires.

Results: Improvements of NRS, WOMAC global, WOMAC pain, WOMAC stiffness, WOMAC function at 3, 6, 12 months were statistically significant in favor of the ACS treated knees. GPA assessment also favored ACS vs Dexamethasone. Adverse events were recorded and are reported herein.

Conclusion: ACS is statistically significant superior to Dexamethasone. Both treatments are safe. Both ACS and Dexamethasone injection treatments significantly improve knee osteoarthritis pain, stiffness and function.

Introduction

Background/rationale

The irreversible, progressive and chronic nature of osteoarthritis (OA), at present, requires chronic management adjusted to the patient's individual needs. Currently approved treatment options are largely palliative, suppressing pain until joint replacement is judged to be unavoidable. There is consensus that early surgery may not contribute to better outcomes [1]. According to OARSI and multiple Cochrane Reviews, the spectrum of currently available treatments is not only limited but lacks appropriate long-term efficacy (e.g. NSAIDs have low Effect Size d [104]. of 0.37 and safety issues) [2-4]. Also, decision-making has entered a phase that endeavors to include patient's opinion, reflecting a desire to reach more generalized acceptance e.g. in Rheumatoid Arthritis

[5]. Similar activities may ensue for OA given the growing medical need. Inflammatory cytokines are seen to be among key drivers in OA cartilage destruction or rheumatoid arthritis [5,6].Further key factors in OA pathology include, but are not limited to, oxidative stress leading to higher concentrations of oxygen and nitrogen radicals which drive inflammation and impair joint homeostasis [7,8]. Chronic ATP deficiency due to mitochondrial dysfunction is part of this condition [9]. Interleukin-1 (IL-1), is one of the key mediators of cartilage destruction, stimulating proteolytic enzyme synthesis and attracting inflammatory cells to the joint and causing hyperalgia [10]. Interleukin-1 receptor antagonist (IL-1Ra) is a natural competitive inhibitor of IL-1 and has been introduced to the market as recombinant IL-1Ra (Anakinra) for the treatment of rheumatoid or other inflammatory pathologies [11].

Gene therapy approaches utilizing the IL-1Ra gene have also been performed and are still experimental [1-11]. An alternative technique to generate IL-1Ra was published by Meijer et al. generating whole blood serum containing high concentrations of autologous IL-1Ra, Autologous Conditioned Serum (ACS) [12]. Publications have also used the terms "autologous IL-1Ra". "Orthokine", "Blood Clot Secretome" or "Blood Cell Secretome" for ACS [13]. This method stimulates autologous cytokine production by whole blood cells in addition to release to saturation of growth factors from platelets. ACS is re-injected into the osteoarthritic joint and other pathologies for pain and functional improvement [14].

ACS contains a plethora of components such as growth factors, cytokines, mitochondria derived peptides, alarmins, lipid mediators, exosomes, and potential radical scavengers [14-16]. It is now interpreted as, or containing a, whole blood secretome. ACS has been studied over more than two decades. The use of ACS has successfully expanded from the treatment of OA and radiculopathy to soft tissue disease (tendon, ligament, muscle injuries and meniscal injuries) and wound treatment [13,14,17-49]. It is now known that local injections with ACS have pain resolving and regenerative properties.

Glucocorticoid injection is among the most popular intra-articular therapies for OA due to its fast action and the lack of serious side effects [50]. Dexa is one well established proponent drug that is known for it's high potency. It is generally accepted that the beneficial effect of intra-articular glucocorticoid injection is immediate but short-lived and is more effective in cases with an inflammatory component [51]. Too frequent use is however frowned upon. OARSI recommendations in 2019 state: Intra-articular glucocorticoids (IACS) are conditionally recommended for acute (1-2 weeks) and short-term (4-6 weeks) pain relief [52].

Objectives

In our clinical experience, glucocorticoid treatment and ACS treatment are equivalent therapeutic approaches. We therefore offer both therapeutic approaches to our patients and inform them about the advantages and disadvantages of both therapies. In some cases of bilateral OA, patients were unable to make a choice between the two therapies. Therefore, in order to allow the patient to make a direct comparison and thus make the best individual treatment decision at subsequent treatments, we have chosen the approach of treating one knee joint with glucocorticoids and the other knee joint with ACS.

As this approach is rather unusual in daily medical practice, we decided to structure this information from our medical records and present it to the public.

Methods

Study design

Monocentric, closed cohort study with relocated baseline and an internal intra-individual matched comparison of left and right knee in a group of 34 patients.

Setting

The treatments were executed at the Shin Kong Orthopedic Sports Medicine Centre of Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, between 2005 and 2006. The observation period was 12 months. Post-examinations were performed after 3, 6 and 12 months.At the initial office visit, thorough and detailed explanation of the procedure, risks, complications, side effects, and potential therapeutic effects were given. The patient's medical history, physical examination, standing X-ray (AP, lateral, and merchant views) were documented in detail. Knee x-rays were evaluated according to the classification of Kellgren and Lawrence (KL) at the time of evaluation.63 In order to obtain a higher objectification of their individual assessment of their symptoms, patients then completed our standard clinical efficacy symptom assessment questionnaires before the intra-articular injections and at each control visit for their respective knee joints.

All 34 patients were injected with ACS in one knee and Dexa in the contralateral knee. For ACS preparation they donated 50 mL of blood into an approved medical device containing medical grade glass spheres (Orthokine®II Set 60 ml, Orthogen, Germany). These medical grade glass spheres are specifically polished, washed and otherwise untreated. They accelerate coagulation. The syringe containing the patient's whole blood was submitted to extended coagulation at 37°C for 24 hours. After extended coagulation, the ACS was recovered by centrifugation and then stored frozen in aliquots at -20°C until injection. Each patient's knees received either (1) a series of 6 (2mL each) injections with ACS twice per week over a three-week period into one knee or (2) a single dose of Dexamethasone-21-Phosphate Disodium 5mg (combined with 1mL of 2 % Xylocaine) into the contralateral knee. Knees were randomly assigned to the respective treatments. ACS treatment regimen was performed as was shown to be successful by Baltzer, et al. and Yang, et al. [27,29]. Each ACS injection was carried out with the use of AcroMed® 0.2 µm/3.2 cm filter (Pall Life Science, Ann Arbor, Michigan, USA).

Participants

The cohort of patients who received ACS in one knee and Dexa

in the contralateral knee was selected for analysis according to the following selection criteria: Male and female patients aged at least 21 years with radiographically documented bilateral osteoarthritic joints (K&L grade I - III), who had not undergone surgery three months prior to treatment and who had not received any additional anti-inflammatory drugs, intra-articular injections or surgical procedures prior to treatment. None of the patients had systemic disease of the musculoskeletal system (i.e., RA or gout), bone cancer, metastasis or tumor-like lesions of the knee, fixed lower limb deformities, history of bleeding disorders or current anticoagulant treatment, presence of hepatitis B or C, HIV 1 and 2 (AIDS virus), syphilis and HTLV I and II or acute infection of the knee. Patients had free access to a daily knee exercise programme, hydrotherapy, physiotherapy, the use of cryotherapy, the use of orthotics, the use of a cane or the use of acetaminophen.

Data sources / Measurements

The investigation was based on our standard clinical efficacy symptom assessment questionnaires patients were asked to complete for their respective knee joints. These questionnaires consist of a numeric rating scale (NRS: 0-10) for pain, Western Ontario and McMaster Universities Arthritis Index (WOMAC scoring by NRS 0-10) and a Global Patient Assessment (GPA) questionnaire. GPA1: "How would you assess the effectiveness of your osteoarthritis treatment at the present time?" answers we given as "poor, unsatisfactory, satisfactory, sufficient, good and very good". GPA2: "How much has the therapy helped your disease?" answers were given in per cent. For NRS pain (Question: "What was your maximum pain in the past two weeks") and WOMAC lower values indicate improved symptoms. An independent third party performed the data input and analysis.

Bias

Bilateral investigations have been criticized but also have been used in clinical and animal OA studies [53-62]. In the presented setting one of the main advantages is that the patient can directly compare the clinical changes in both knees and choose their own therapy for subsequent treatments. However, this advantage also implies the risk of a very individual ability to differentiate symptoms between the two knee joints and carries the risk of information bias, which cannot be excluded. Another risk is that, due to the lack of randomised allocation of therapy, a more severely affected knee may have been more likely to receive a particular therapy, leading to differential (non-random) misclassification. Nevertheless, an important advantage of this methodological approach is that the risk of common types of bias, such as selection, detection or recall bias, is not necessarily anticipated.

Study Size

The study size of 34 subjects represents the total number of patients over a two-year period who meet the selection criteria for analysis. This may seem too small, but the intra-individual matching reduces the variability in the statistical analysis, which in turn leads to a more precise statement about the effects.

Statistics

Statistical analysis was performed using descriptive methods and inferential analysis using appropriate significance tests. Missing values were not imputed. A two-tailed t-test for paired data was used to calculate probabilities for continuous data. A local p-value ≤ 0.05 was considered statistically significant [64].

Results were interpreted in a confirmatory manner. Statistical analysis was performed with SPSS version 24.0.

Results

Participants

During the 2-year period, a total of 35 patients were eligible and screened for eligibility. One patient did not meet the selection criteria, so 34 were considered eligible and included in the study. All of them passed the control visit and were included in the analysis.

Descriptive data

Characteristics of study participants are displayed in Table 1.

Main Results

WOMAC global improvement of 36% was defined to be clinically relevant. It was reached for Dexa treated knees at month 12 and for ACS treated knees at months 3, 6 and 12 (Table 2). ACS and Dexa baseline scores were statistically significant different for NRS (p=0.01) and WOMAC pain and global (p=0.015; p=0.017). ACS started off with worse baseline than Dexa and showed WOMAC global intra group effect sizes 1.28, 1.32 and 1.4 at 3, 6 and 12 months respectively. Dexa showed intra group effect sizes of 0.47, 0.66 and 0.7 at 3, 6 and 12 months respectively (Table 3). A graphic display of the evolution of NRS graded pain (Figure 1) and the evolution of WOMAC global score (Figure 2) over time shows that both groups appear to benefit from the respective injection treatment. Both ACS and Dexa treated knees experienced statistically significant intra-group improvement of symptoms at 3, 6 and 12 months by NRS, WOMAC (Tables 2 and 3) and GPA (Figures 3 & 4). ACS treated knees performed significantly superior to Dexa at all follow-up evaluations. Matzkin et al. published a (rather high) 21.7% WOMAC global improvement vs baseline as the minimal clinically important difference (MCID) cutoff in a trial evaluating the efficacy of 1 mL of triamcinolone 10 mg and 4 mL of 1% lidocaine until 6 months follow up [105]. Table 3 shows that both groups in the present study fulfill this criterion at all follow up time points.

By GPA, over all follow ups of ACS knees, 55.9% of the patients rated the treatment as good to very good, 32.4% as sufficient to satisfactory, and 11.8% as poor or unsatisfactory. 64.7% of patients had 60 to 100% improvement in their disease, 17.6% had 20 to 60% improvement, and 17.6% had almost no improvement. Of the Dexa knees, 26.5% of the patients rated the treatment as good to very good, 58.8% as sufficient to satisfactory, and 14.7% as poor or unsatisfactory. 35.3% of patients rated the Dexa treated knees with 60 to 100% improvement in their disease, 38.2% with 20 to 60% improvement, and 26.5% with almost no improvement. No serious complications were observed (Table 4). The adverse events

did not have clinical impact; all side effects were mild and resolved spontaneously within a few hours (minor swelling, discomfort, soreness, mild pain, stiffness, and knee pain). Pain at injection site was the most frequent adverse effect in the ACS (1.96% of interventions) knees. Soreness at injection site (14.71%) was most frequent adverse effect in the Dexa interventions.

Table 1: Characteristics of study participants.

	N (%)
Total patients	34 (100%)
Total knees	68 (100%)
Male	11 (32%)
Female	23 (68%)
OA (K&L grade)	
K&L grade I	19 (56%)
K&L grade II	6 (18%)
K&L grade III	9 (26%)
Mean (min-max)	
Age (years)	61.3 (36 - 79)
Height (cm)	162.1 (148 - 184)
Weight (kg)	67.8 (44 - 144)
Symptoms (months)	72.9 (4 - 240)

Table 2: Clinical responses between baseline and months 3, 6 and 12 for patients treated with ACS or Dexa. In both groups, the clinical responses were significantly improved after 3 months and the improvement continued at 6 and 12 months. Percentage of improvement is given. ACS meets the predefined score improvement of 36% (as a measure of therapeutic success) for all parameters and time points. Dexa meets the predefined score improvement for parameters NRS at 12 months, WOMAC stiffness at 6 and 12 months and for WOMAC function at 12 months.

Table 2. Changes in clinical responses between baseline and 3, 6, 12 months by treatment groups						
	Baseline to 3 months		Baseline to 6 months		Baseline to 12 months	
ACS	**Mean ±SD**	**p-value**	**Mean ±SD**	**p-value**	**Mean ±SD**	**p-value**
NRS	-3.8 ±2.7	<.001	-3.6 ±2.5	<.001	-3.8 ±2.2	<.001
% change	-59.4%		-56.3%		-57.8%	
WOMAC pain	-12.1 ±8.6	<.001	-12.6 ±8.2	<.001	-12.6 ±10.0	<.001
% change	-56.5%		-58.8%		-58.3%	
WOMAC stiffness	-5.4 ±5.3	<.001	-6.0 ±5.0	<.001	-6.3 ±6.8	<.001
% change	-58.1%		-64.5%		-67.7%	
WOMAC function	-41.0 ±37.2	<.001	-43.6 ±33.7	<.001	-47.1 ±37.7	<.001
% change	-55.6%		-59.1%		-63.8%	
Dexa	**Mean ±SD**	**p-value**	**Mean ±SD**	**p-value**	**Mean ±SD**	**p-value**
NRS	-1.2 ±1.1	<.001	-2.0 ±2.5	<.001	-2.2 ±2.3	<.001
% change	-22.0%		-35.6%		-39.0%	
WOMAC pain	-4.2 ±6.5	<.001	-6.1 ±7.6	<.001	-6.6 ±9.6	<.001
% change	-23.5%		-31.1%		-32.7%	
WOMAC stiffness	-2.7 ±3.9	<.001	-3.7 ±5.4	<.001	-4.1 ±6.0	<.001
% change	-30.3%		-39.3%		-43.8%	
WOMAC function	-17.6 ±26.1	<.001	-24.1 ±33.0	<.001	-27.4 ±35.7	<.001
% change	-25.6%		-32.6%		-37.5%	

Table 3: Differences between ACS and Dexa treatment groups at 3, 6 and 12 months (NRS, WOMAC global, WOMAC pain, WOMAC stiffness, WOMAC function) were significantly better for ACS. Effect size (ES, Cohen's [104].) vs baseline is shown for WOMAC global with medium values for Dexa and large values for ACS. Percentage of improvement at follow ups is given for WOMAC global. Effect sizes [104] between groups are 0.62, 0.49 and 0.45 in favor of ACS at 3, 6 and 12 months.

Mean clinical scores at baseline, 3, 6 and 12 months for knees treated with ACS or Dexa					
		Baseline	**Month 3**	**Month 6**	**Month 12**
		Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**
NRS	**ACS**	6.4 ±2.4	2.6 ±2.1	2.8 ±2.2	2.7 ±1.9
	Dexa	5.8 ±2.7	4.6 ±2.3	3.8 ±2.0	3.6 ±1.9
	p-value	=0.01	<0.001	=0.009	=0.029
WOMAC global [0-240]	**ACS**	104.7 ±51.2	46.1 ±39.2 -55% ES 1.28	42.5 ±42.3 -59.4% ES 1.32	38.7 ±42.1 -63.0% ES 1.4
	Dexa	98.7 ±53.7	74.1 ±50.5 -25% ES 0.47	64.7 ±48.7 -34.4% ES 0.66	60.6 ±54.5 -38.6% ES 0.7
	inter group comparison	=0.017	<0.001 ES 0.62	<0.006 ES 0.49	<0.001 ES 0.45
WOMAC pain [0-50]	**ACS**	21.6 ±10.5	9.4 ±2.1	8.9 ±9.0	9.0 ±10.4
	Dexa	19.3 ±11.3	15.1 ±8.5	13.1 ±9.2	12.7 ±10.5
	p-value	=0.015	<0.001	=0.006	=0.019
WOMAC stiffness [0-20]	**ACS**	9.3 ±6.2	3.9 ±4.6	3.3 ±3.8	3.0 ±3.5
	Dexa	9.1 ±6.3	6.4 ±5.5	5.4 ±4.3	4.9 ±4.5
	p-value	=0.263	<0.001	=0.005	=0.003
WOMAC function [0-170]	**ACS**	73.8 ±37.2	32.8 ±27.5	30.2 ±30.4	26.7 ±29.0
	Dexa	70.3 ±39.2	52.7 ±38.3	46.2 ±36.7	42.9 ±40.3
	p-value	=0.053	<0.001	=0.009	<0.001

Table 4: Frequency of adverse events in ACS and Dexa treatment as per number of injections. All events were classified as "mild".

	Dexa		**ACS**	
	N	%	N	%
Number of injections	34	100	204	100
Adverse events				
Mild swelling	1	2.94	3	1.47
Discomfort at injection site	0	0.00	2	0.98
Soreness at injection site	5	14.71	3	1.47
Pain at injection site	2	5.88	4	1.96
Tightness	0	0.00	2	0.98
Knee Pain	1	2.94	1	0.49
Total adverse events	9	26.47	15	7.35

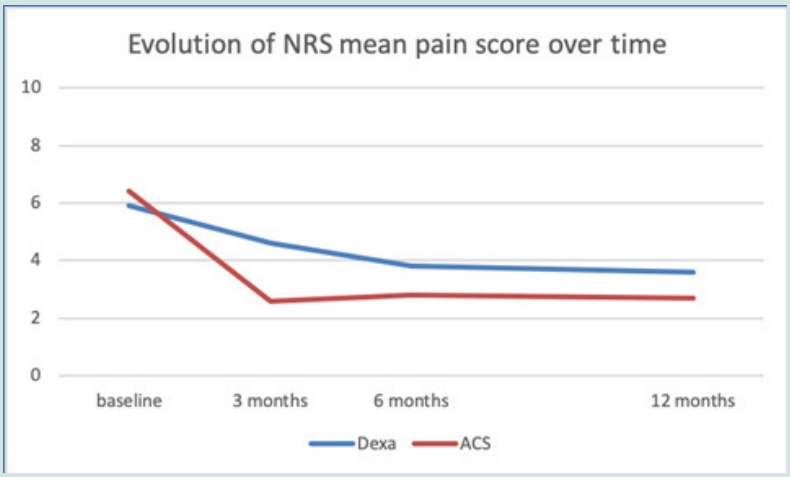

Figure 1: Numeric rating scale (NRS 0-10) pain evolution from baseline to 12 months follow up. Patients were asked: "What was your maximum pain in the past two weeks"? Differences between groups were statistically significant at all time points (p≤0.5).

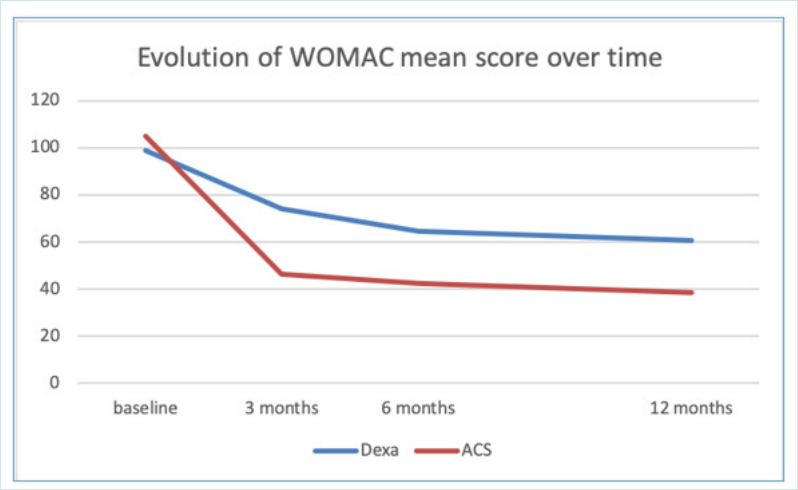

Figure 2: Western Ontario and McMaster Universities Arthritis Index (WOMAC) evolution from baseline to 12 months follow up. WOMAC global improvement of 36% was defined as clinically relevant. This target was reached for Dexa treated knees at month 12 and for ACS treated knees at months 3, 6 and 12. Note: here, the WOMAC global score ranges from 0-240. In this graph, the vertical axis is truncated at 120. Differences between groups were statistically significant at all time points (p≤0.05).

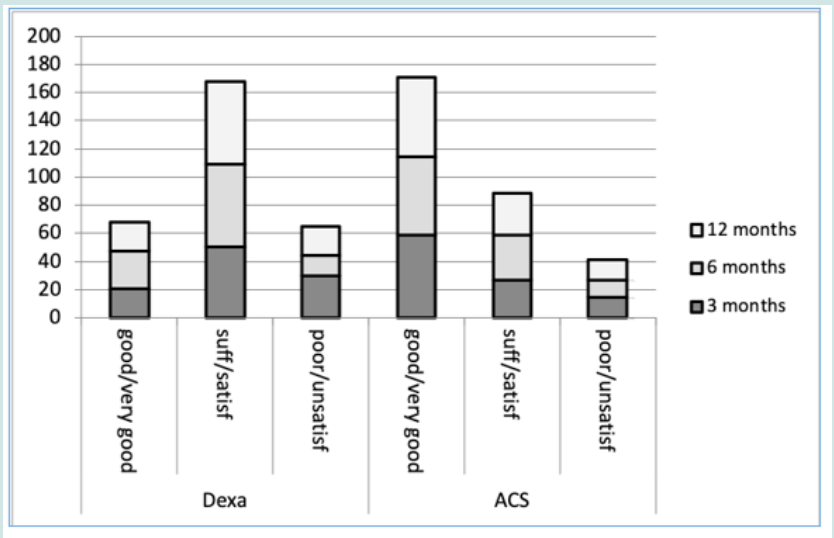

Figure 3: GPA1. Patients were asked: "How would you assess the effectiveness of your osteoarthritis treatment at the present time?" Patients chose between improvements: poor, unsatisfactory, satisfactory, sufficient, good and very good.

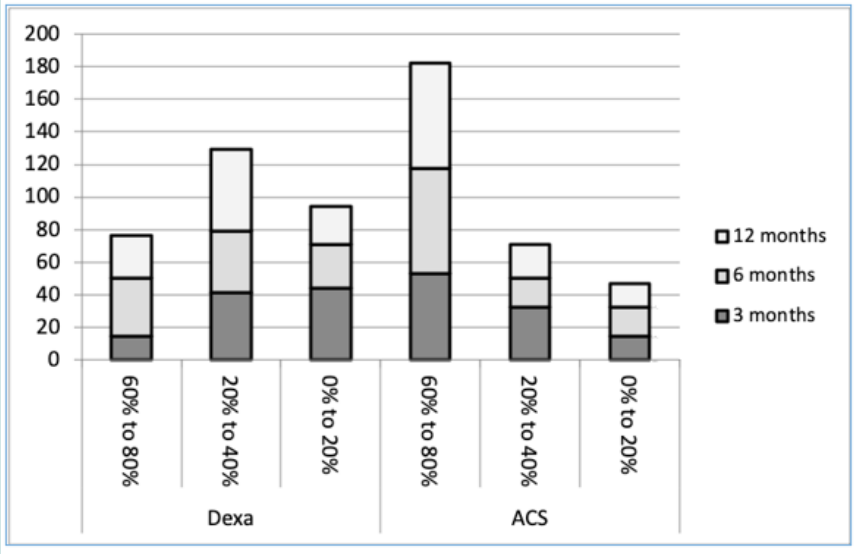

Figure 4: GPA2. Patients were asked: "How much has the therapy helped your disease?" Answers were given in per cent (%).

Discussion

Limitations

Important limitations of this study are retrospective analysis, the small number of patients and the asymmetry of the treatment protocols due to the treatment in 2005. The higher number of injections of ACS vs one in the Dexa knees may have biased the outcomes. Also, the bilateral knee treatment may have influenced the patients' scoring of the respective knees. Baseline scores NRS, WOMAC pain and WOMAC global were statistically significant better in the Dexa group. >60% of patients were KL grade I and none were grade IV. Finally, the extent of pain medication and use of physical therapy of each patient was not quantitated, but possibly would not have affected outcome since it would have had effect on both knees.

Key Results

In this cohort of patients with bilateral knee osteoarthritis injection of 6 doses ACS in one knee produces statistically significant better outcomes than one injection of Dexamethasone in the contralateral knee.

Interpretation and Generalizability

In studies performed elsewhere ACS has been compared to placebo, Hyaluronan (HA), platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), ozone, dextrose prolotherapy, and glucocorticoid [24-33,37,39,41,42,44-46,49].The authors of this current paper compared a standard routine of Dexa (5mg, one time) injection against an established protocol of ACS injection (6 injections of 2mL serum) in bilateral OA knees with K&L grade I to III changes. Dexa has been favorably evaluated for inflammation-induced posttraumatic joint injury, preventing cartilage damage [65]. Data for ACS presented here confirm results by other groups with significant score improvements in RCT and non-RCT studies [17-27,29-35,37-49]. An exception is Yang et al. who reported weaker outcomes when ACS was compared to placebo [27]. Local injection with ACS has also shown significant benefit in other orthopedic and non-orthopedic indications, including back pain, tendinopathy, muscle injury, wound healing, meniscal pain and post-surgical treatment of ACL-reconstructed knees [34,35,37-49].

To put these results in perspective: Khurana et al. compared PRP (processed by laboratory protocol) to HA (Synvisc-one), depot-Methylprednisolone (depot), and a matched ACS cohort with follow up at 6 months [25]. They conclude that intra-articular injections of ACS and PRP are superior to HA and steroids in terms of clinical outcomes. Between PRP and ACS the difference by VAS and WOMAC (ES 0.41 and 0.82) was in favor of ACS. Notably, the small response rate in the depot group at 6 months contrasts with our finding of 34% pain relief at 6 months in the present manuscript. In perspective, "placebo effects" of up to 35% primary score improvement have been reported in other intra-articular injection studies and were considered valid, sometimes reaching large effect sizes for invasive (e.g. injections) OA treatments [65-70].

Glucocorticoid injections for more than four times annually are generally not recommended [52]. McAlindon, et al. showed that Triamcinolone 40mg, injected 4 times annually, led to a significant decrease of i.a. cartilage volume after 2 years. The authors confirmed that intra-articular injections of Triamcinolone should be used prudently [71]. Some authors have criticized McAlindon's protocol since Triamcinolone (40mg) is mainly indicated "to tide over" an inflammatory episode and not as a regular OA injection therapy independent of symptoms [72]. In the current study the authors used only one injection of 5mg Dexa.

It is commonly acknowledged that glucocorticoids have a transient symptomatic effect for up to 6 weeks on osteoarthritic joints [52]. Data in this study show a prolonged clinical effect of up to 12 months. Patients were treated in a clinical setting with easy access to hydrotherapy and physical therapy. The continued effect of steroid injection at 12 months after injection may be partly explained by the devotion of patients to daily knee exercise regimen,

hydrotherapy, physical therapy, and the use of cryotherapy. Baselga and Hernandez have described very good (ES >5) clinical results when patients enjoyed 30 sessions of intensive physiotherapy after 4 ACS injections [23]. This finding supports the consensus on physical therapy for OA patients. Knee stiffness improvement, in our study, was between 30% and 67%. This might also be due to daily knee exercise regimens. However, such activities were not quantitated.

Another explanation for the prolonged effect of glucocorticoid in this study might be a possible effect of ACS on the contralateral knee, possibly through a neurologic mechanism. Physical interventions in humans and biological (gene) therapy in animal experiments have produced evidence for a contralateral effect affecting clinical symptoms in a non-treated limb or organ [73-79]. ACS might have supported the glucocorticoid effect on the contralateral knee. Creamer compared the effects of intra-articular bupivacaine injection versus placebo. With his small sample size (N=10 in each group), the contralateral non-injected knee had decreased pain at 7 days after injection in the bupivacaine group [80]. However, the placebo group did not have any reduction of pain in either knee, therefore, the study failed to detect a placebo effect. He attributed the reduction of knee pain to the release of neurotransmitters by the synovium, which in turn synapsed with afferent neuroreceptors of the contralateral knee in the spine.

In transgenic studies, contralateral joint effects have been attributed to transduced leukocytes, circulating transgenic product or immunomodulatory effect of circulating transduced dendritic cells [81]. In Brandt's randomized study comparing intra-articular HA injection to saline, he did not notice any contralateral effect of either group [82]. In fact, he noticed an actual increase in pain in the contralateral knees of both groups at 27 weeks after injection. Kim et al. discussed that exosomes produced by dendritic cells may account for a positive contralateral effect, representing a novel, cell-free agent influencing immune dysfunction [79]. Incidentally, extracellular vesicles including exosomes are a common component in body fluids, plasma or serum, including ACS.

Osteoarthritis symptoms are not well understood. Cartilaginous changes at times do not correlate well with pain and dysfunction while inflammation and changes in synovium and/or bone may do so [83-86]. Dexa is a potent and fast acting anti-inflammatory agent, ACS is thought to have a slower, more profound effect. The high number of 6 injections in the ACS knees is cumbersome but is in line with references 27 and 29. However, successful ACS treatment regimens with smaller numbers of injections (minimum 3) and smaller volumes (minimum 1mL) of injected serum have been published [18,23]. With regards to other Orthobiologics' safety and reproducibility, ACS has advantages over the popular autologous platelet-rich plasma (PRP) for orthopedic indications. [13,32] ACS quality depends on the starting conditions (e.g., blood cell counts) and standardized extended coagulation conditions. ACS profoundly improves intra-articular homeostasis improving oxidative stress, and both cytokine balance IL-1Ra over IL-1b and autogenous Hyaluronic Acid content [13]. Interestingly, a recent study with i.a. PRP-resistant knee OA patients showed that ±2/3 responded well to i.a. ACS injection [22] Shirokova, et al. compared 6 injections of ACS or PRP in a prospective, non-randomized, open-label study and found that at the 3-month follow-up, clinical efficacy (VAS and WOMAC) improved significantly for both groups, but ACS had a more significant reduction from baseline to 3 months [13]. Furthermore, between the one-and three-month follow-up, ACS efficacy further increased, whereas PRP efficacy decreased. PRP did have a positive clinical effect in joints with "subclinical synovitis" (not inflamed), while joints with "moderate synovitis" (inflamed) did not have a clinical effect. This was the first study to investigate the biochemical effects of ACS vs PRP. Synovial fluid viscosity improved significantly more with ACS than in the PRP group. Cytokines IL-1Ra and IL-1b ratio was significantly stronger in the ACS group than in the PRP group. The authors concluded that ACS was clinically and biochemically superior to PRP and met the Minimal Clinically Important Improvement (MCII) criteria for VAS in knee OA. Adverse events with intra-articular PRP injections have been reported [87,88], however, in many PRP studies, adverse events are briefly described as "self-resolving" and "transient". This lack of detail in reporting is common and, frankly, disquieting. It appears that a PRP-related flare that may take up to a week to resolve is accepted as part of the treatment. Stanford Medical Center has a clear statement that 1 in 10 patients experience a flare with intense pain (accessed 2023-01-27 [89] The Integrative Medicine Center of Western Colorado mentions 1 in 20 patients with post-injection flare that resolves within "a few days" [90]. A literature search identified papers that describe possible mechanistic reasons for such caveats [87-103].

Conclusion

The authors conclude that in this study ACS treatment is clinically significant more potent than Dexa. Both ACS and Dexa are safe and effective for intra-articular treatment of grade I to III bilateral knee OA. The clinical efficacy of Dexa injections was unexpectedly long.

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Declaration of Conflict of Interest

NH, JL and DH declare no conflict of interest in preparing this article. JR works with Dr. Wehling & Partner, Germany.

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