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Does Autologous Conditioned IL-1 Antagonist (ACS) Reduce Pain in Patients with OA or Lumbar Radiculopathy?

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ABSTRACT

Objective: To determine whether or not Autologous conditioned IL-1 antagonist (ACS) reduce pain in patients with OA or lumbar radiculopathy.

Study Design: Review of 3 randomized, double-blind controlled clinical trials in 2007, 2008, and 2009, all in English.

Data Sources: Two randomized, double-blinded controlled clinical trials comparing the effectiveness of intraarticular injections of an autologous IL-1 receptor antagonist solution versus a control in OA and one randomized, double-blinded controlled clinical trials comparing autologous IL-1 receptor antagonist epidural injection versus 5 and 10 mg triamcinolone in patients with lumbar radiculopathy.

Outcomes Measured: The outcomes in this study were measured using the Western Ontario and McMaster Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS), and the Oswestry Disability Index (ODI).

Results: Baltzer et al. determined a statistically significant reduction in OA-related pain when compared to both saline and hyaluronic acid. Yang et al. failed to show pain reduction in ACS-treated patients when compared to placebo. Becker et al. reported significant reductions in pain, but were not statistically significant when compared to the control arm.

Conclusion: Results of the mentioned studies proved that ACS does decrease pain in patients with OA and LR; however, this pain reduction was not universally statistically significant and thus requiring further, more uniform trials. The Baltzer et al. results were encouraging, however, and do warrant future investigation.

Keywords: Orthokine, Interleukin-1 inhibitor, autologous conditioned serum, osteoarthritis.

Introduction:

Osteoarthritis (OA) – an inflammatory condition of the bone caused by recurrent force and trauma – and lumbar radiculopathies – excessive radicular pain caused by lumbar disc degeneration and stenosis – are pervasive, often disabling, and degenerative conditions that lead to recurrent pain and loss of function. OA and lumbar radiculopathies (LR) affect approximately 27 million people and 1/100 adults in America, respectively.[1,2] Even more concerning, the estimated lifetime risk of developing symptomatic OA in a patient's lifetime is ~45%.[2] OA and lumbar radiculopathies are degenerative processes that do not resolve, often requiring constant medical intervention. The average annual disease cost for each OA patient is ~ $5,700 a year, while the total annual inpatient cost for treating OA reached $48 billion in 2008.[2] The average number of knee replacements per year is estimated to rise 673% from 2004 to 2030, or from 478,000 to 3.48 million, respectively.[2]

The exact mechanism of both disease processes are well documented and understood. OA of the knee develops due to a failure in its protective mechanisms, leading to joint injury. More specifically, constant strenuous force on the joint leads to the wearing down of cartilage, making the bone susceptible to damage. In response to this damage, the bone becomes sclerotic and forms osteophytes, which grow through the cartilage and cause increased mechanical friction and damage. Lumbar radiculopathy, on the other hand, is not a pathology itself, but more a sequelae of an underlying disorder, those typically being degenerative disc disease or spinal stenosis, both of which are due to improper body mechanics and persistent degenerative forces.[1] Symptoms of OA include pain localized to the specific joint, pain that worsens with activity and is relieved by rest, and acute and intermittent flare-ups (especially with humidity). Symptoms for LR include shooting pain and numbness in the lower back, groin, buttocks, and legs.

Currently, there are many treatment options for OA, including dietary regimens, wearing barefoot or minimalist shoes, and pharmacological or surgical interventions.[3,4] Common pharmacological approaches include analgesics (acetaminophen, NSAID's, or Cox-2 inhibitors), codeine, topical creams (analgesics or capsaicin), intraarticular injections (corticosteroids, hyaluronic acid (HA), or platelet-rich plasma (PRP), though none of these treat the underlying pathology. Surgical options include arthroscopic debridement and total joint replacement. For lumbar radiculopathies, the available treatments are non-pharmacological (physical therapy, weight loss, and activity modification), pharmacological (NSAID's or epidural corticosteroid injections), and surgical (laminectomy or spinal fusion).

Due to the limited efficacy and adverse effects of current pharmacological approaches, reluctance to make substantial lifestyle and dietary changes, along with the numerous risks associated with surgical interventions, patients and researchers are searching for new pharmaceutical alternatives. Within the past decade, researchers in Germany have developed an intraarticular injection championed by a litany of professional athletes: Autologous conditioned serum (ACS). ACS – an autologous conditioned IL-1 receptor antagonist (IL-1Ra) – is produced by removing blood from a patient, placing the blood in a test tube with glass beads that activate IL-1Ra leukocytes, and centrifuging the products to isolate the leukocytes.[5] The targeting of IL-1 is a novel approach because it is a cytokine known for its pro-inflammatory properties. Researchers believe that by decreasing IL-1 production, they will be able to inhibit the damage wrought by inflammation in OA and LR. The purpose of this study is to analyze the utility of ACS in the treatment of OA and LR.

Objective:

The objective of this selective EBM review is to determine whether or not "Autologous conditioned IL-1 antagonist (ACS) reduce pain in patients with OA or lumbar radiculopathy?"

Methods:

The studies in this analysis included 3 double-blinded, RCT's where the patient population ranged from 84 to 376 for the *Becker et al. (*2007*) and Baltzer et al. (*2009*)* studies, respectively. The interventions for the OA studies both included intraarticular injections of an autologous IL-1 receptor antagonist solution; however, *Baltzer et al.* included, along with the control, a comparative arm of HA. The intervention studied by *Becker et al.* (2007) was an autologous IL-1 receptor antagonist epidural injection versus 5 and 10 mg triamcinolone as the controls. The injection schedule was once per week for 3 consecutive weeks in the *Baltzer et al. (2009)* and *Becker et al. (2007)* studies, whereas the *Yang et al. (2008)* study interventions occurred on days 0, 3, 7, 10, 14, and 21. Inclusion and exclusion criteria, amongst other study demographics and characteristics are listed in Table 1 below.[6.7.8]

Key words used in searches included "Interleukin-1 inhibitor and autologous conditioned serum" and "Autologous interleukin-1 and osteoarthritis." All articles were published in English in peer-reviewed journals. Articles were searched online via PUBMED, OVID, and google and were selected based on relevance to the clinical intervention being assessed and the inclusion of patient-oriented outcomes (POEMS). Inclusion criteria for the articles selected included studies that were randomized, controlled, and double-blinded, whereas exclusion criteria consisted solely of patients under 18 years of age. The statistics reported in the studies included Chi-square, p-value, and analysis of variance one-way method (ANOVA).

Table 1: Demographics and characteristics of patient populations by study

Study	Type	# Pts	Age, yrs	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Balzter et al. (2009)[4]	Double blind RCT	376	≥30	-Dx w/ primary OA for at least 3 months - Willing to d/c all analgesia and NSAIDs for ≥ 6 months	- Grade IV OA - Systemic or inflammatory joint ds - Bone CA or mets near joint - Pregnant or lactating, alcohol/drug abuse	31	Intraarticular injections of autologous IL-I receptor antagonist vs. HA once/wk x 3 weeks
Becker et al. (2007)[5]	Double blind RCT	84	≥29	- Unilateral lumbar radicular compression - Clinical dx confirmed by MRI or CT showing herniation - Pain duration must be 6 weeks≥	- Pts needing early surgery b/c of paresis or unbearable pain - Neurological illness - Cervical myopathy - Systemic bone or joint illness - Cortisone or opiod use in the last 6 months	1	Autologous epidural perineural interleukin-1 receptor antagonist injection vs 5 or 10 mg triamcinolone once/wk x 3 weeks
Yang et al. (2008)[6]	Double blind RCT	182	≥18	- Clinical evidence of OA - Knee complaints surpassing the threshold indicated on WOMAC, KOOS, or VAS	- Overall poor general health - Suspicion of ipsilateral coxarthrosis and hip prosthesis loosening - Alcohol/drug abuse - OA grade IV - Known immunodeficiency - Known coagulopathy - Corticosteroid and anti-coagulant usage or morbid obesity	9	Intraarticular injections of autologous IL-I receptor antagonist vs placebo on days 0, 3, 7, 10, 14, and 21.

Outcomes measured:

The outcomes in this study were measured using the Western Ontario and McMaster Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS), and the Oswestry Disability Index (ODI). The WOMAC is comprised of 24 items subdivided into 3 categories: Pain, stiffness, and physical function.[9] The KOOS, on the other hand, consists of 5 different categories: Pain, other symptoms (such as a grinding sensation or knee 'clicking'), function in daily living, function in sports and recreation, and knee related

quality of life. These 5 categories are added to give a value of 0-100, with 100 indicating no symptoms. The VAS simply measures a patients pain level on a scale from 0-100, with 100 being the highest possible pain. The final analysis modality, the ODI, assesses how much an individual is affected by lower back pain via 10 criteria and scaled from 0-100%, with 0% being minimal interference with daily life and 100% being completely bedbound.[10] The WOMAC, KOOS, and ODI are determined by questionnaires filled out by patients, while all 4 analytical modalities are subjective and thus subject to variability and human error.

Results:

The Yang et al. study included 167 patients, with 89 receiving the ACS treatment, while78 received the placebo. Of the 167 patients that received an injection, 80 and 74 patients completed the study for the experimental and control arms, respectively; both accounting for an 84% retention rate. Follow-up duration was 12 months, with patient reporting every 3 months. Both the treatment and control arms exhibited a significant improvement in all analytical modalities when compared to baseline ($P<.001$). The only statistically significant improvements seen in ACS-treated group versus the placebo group was in the KOOS Symptomology ($P = 0.002$) and KOOS Sport ($P = 0.042$). These data points were continuous and summarized in a graph and thus unable to be obtained for analysis. The differences in pain reduction between the experimental and control arms on the VAS was not statistically significant and can be seen in Table 2 below. The most significant adverse event was knee irritation following injection (orthokine = 70 vs. placebo = 67). The NNH could not be calculated because this was not dichotomous data.[8]

Table 2: VAS results for ACS-treated patients versus placebo.

Orthokine	VAS, mean	SD
Baseline	59.68	20.2
3 months	43.63	26.5
6 months	48.59	28.5
9 months	48.91	27.7
12 months	47.32	28.0
Placebo	VAS, mean	SD
Baseline	63.44	18.2
3 months	47.51	26.5
6 months	49.06	27.4
9 months	50.79	25.4
12 months	49.76	26.7

The Baltzer et al. study 376 patients who underwent at least one intraarticular injection. Of those 376 patients, 134 were treated with ACS, 135 with HA, and 107 with saline. The number of patients who completed the trial were 126 (94%), 120 (89%), and 99 (93%) for the ACS, HA, and saline groups, respectively. Follow up duration was 26 weeks, with patients reporting on weeks 7, 13, and 16. All results for pain in the WOMAC and VAS analysis were statistically significant for the ACS-treated group when compared to the control groups (Table 3). Furthermore, there were no statistically significant differences appreciated between the HA and saline groups for any of the WOMAC scores (P>.05). Adverse events were seen in 23%, 38%, and 28% of the ACS, HA, and saline-treated groups, respectively. The main ADR for all groups was localized pain and irritation and accounted for 79% of the total amount of all ADR's. Again, the NNH could not be calculated because this was not dichotomous data.[6]

Table 3: Statistically significant effects for pain in the ACS-treated group versus controls. Results determined from last visit minus baseline.

Variable	P-value	Comparison	Significance
$WOMAC_{pain}$	.001	ACS-Saline ACS-HA HA-Saline	Yes Yes No
VAS	.001	ACS-Saline ACS-HA HA-Saline	Yes Yes No

The Becker et al. study was comprised of 84 patients, with 32, 27, and 25 patients being treated with ACS, 5 mg triamcinolone, and 10 mg triamcinolone, respectively. It is not clear how many patients from each group finished the trial. Follow up duration was 22 weeks, with patients reporting at 6, 10, and 22 weeks. It was found that all treatment modalities exhibited statistically significant changes from baseline in both the VAS and ODI at all time points. At the end of the study, the ACS group showed a statistically significant difference when compared to the 5 mg, but not the 10 mg, triamcinolone group ($P<0.046$). There was a total of 1 ADR for each group, which was a headache at the time of injection.

Discussion:

The main purpose of this meta-analysis was to determine if ACS reduced pain in patients with OA and LR. A careful review of the data presented shows conflicting results for OA. In the Yang et al. study, pain was not significantly reduced in the experimental group when compared to the control group; in fact, the control group performed almost just as well as the experimental group when NSAID's were discontinued. This was a unique and unexpected result, as one would not expect the cessation of NSAID's to decrease pain in the following months. Though there is no literature to support NSAID-induced hyperalgesia, the medical community is replete with

studies on the effects of opiod-induced hypersalgesia. A future study comparing NSAID-induced hyperalgesia versus opiod-induced hyperalgesia would be a valuable tool to either confirm or refute this theory.[13]

On the other hand, data from the *Baltzer et al.* trial is highly convincing of the benefit ACS intraarticular injections have on pain when compared to HA and placebo. For the entire duration of the trial, ACS-treated patients faired significantly better on both the VAS and $WOMAC_{pain}$ scale when compared to the other 2 treatment modalities. It should be noted that in this study patients were forced to discontinue the use of analgesics 3 weeks prior to the commencement and up until the end of the trial. Again, one has to wonder about the possibility of NSAID-induced hyperalgesia. It should also be noted that there were some methodological differences between the two studies. *Baltzer et al.* utilized 6 intraarticular injections over a 3 week period, while *Yang et al*. performed only 3 injections over the same time period.

The *Becker et al.* study analyzing the effects of ACS versus triamcinolone injections for LR failed to show statistically significant benefits overall. It appeared that 10 mg of triamcinolone was just as effective as ACS. As a result, treatment with ACS does not appear to be cost-effective when compared to triamcinolone ($7400 vs. $1850 per injection).[14,15] It is also important to note that ACS is considered an experimental therapy and is thus not covered by medical insurance.

Limitations were present for each study and may have affected the clinical outcomes. All 3 trials had small patient populations, ranging from 376 to 84. Such a small sample size can skew data, as outliers often impart a greater impact on results. This was even noted in the Becker et al. trial, where the mean and median figures for the experimental group were markedly different, leading to skewed data. Furthermore, the studies utilized subjective tools to measure patient pain,

rendering them liable to patient bias. The patient population was also highly variable, as there are different grades of OA. It is possible that certain grades are more responsive to treatment than others.

Conclusion:

ACS does appear to decrease pain in patients with OA and LR; however, evidence is not conclusive as to how effective the treatment is versus other modalities. As a result, further research is warranted prior to determining the cost-effectiveness of this therapy, especially when considering it is not yet an approved therapy in the US and thus not covered by health insurance. Future studies should attempt to replicate that of the *Baltzer et al.* trial, as that appeared to have the most success in ameliorating pain. Furthermore, a study elucidating the most effective schedule for intraarticular injections would be recommended prior to implementation of this strategy.

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