Autologous Conditioned Serum in Lumbar and Cervical Radiculopathy: A Systemic Review

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Abstract

Background: Intervertebral disc degeneration causing radiculopathy is driven by catabolic cytokines like IL-1β and TNFα. Autologous conditioned serum (ACS) was found to be rich in IL-1Ra (Interleukin-1 Receptor Antagonist), and thus, can impede disc degeneration. A systematic review of available literature was conducted to ascertain the potential therapeutic application of ACS in radiculopathy.

Methods: Systematic literature reviews were conducted in PubMed, Scopus and Embase databases, up to September 2020. Randomised controlled trials (RCTs), prospective, retrospective studies and case series with lumbar or cervical radiculopathy and reporting use of ACS were included, with at least one of the outcome measures like VAS (Visual Analogue Scale) for pain, SF-12 (Short Form of Health Survey-12), Oswestry Disability Index, with a minimum follow up of 3 months. Animal studies, abstracts, review articles and case reports were excluded.

Results: A total of four studies, including 107 patients who received ACS were included based on the eligibility criteria. Two were RCTs and two were prospective non-comparative studies. Three studies evaluated the effect of IL-1Ra on lumbar radiculopathy and one on cervical radiculopathy. The mean age of patients in the studies ranged from 37.15 to 53.9. The dose of ACS used was 2–4 mL injection. In 1 RCT, methylprednisolone was used as control, in the other 5 mg and 10 mg triamcinolone was used. All studies reported a statistically significant reduction in pre-injection and post-injection VAS, there was also a

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significant difference as compared to 5 mg triamcinolone. Three studies reported significant improvement in ODI. Two studies reported statistically significant improvement in SF-12 scores post injection ($p < 0.001$). For cervical radiculopathy, Neck pain disability score showed a decrease of 73.76% from pre-injection to final follow up and Neck disability index showed a decrease of 74.47%.

Conclusion: All of the four studies concluded that epidural perineural injection with ACS, reduced pain scores (VAS, NPDS) and improved functional scores (ODI, SF-12 and NPDS), as compared to placebo and other conventional therapeutic modalities like steroids, and analgesic-anaesthetic-steroid cocktail. Hence, ACS is a promising new therapeutic modality in both lumbar and cervical radiculopathy, and further studies can strengthen the present evidence regarding its efficacy and safety profile.

Keywords

Chrononutrition · Precision medicine · Metabolic surgery · Predictive genetics · COVID-19

4.1 Introduction

Low back pain is one of the most common presenting complaints that orthopaedic surgeons come across. It affects approximately 23% of the world population, with the majority being females in the age group 40–80 years (Hoy et al. 2012). Neck pain is the fourth leading cause of disability worldwide, with an annual prevalence of more than 30% (Cohen 2015). Lumbosacral radiculopathy and cervical radiculopathy are defined as low back pain and neck pain, respectively, due to irritation or compression of nerve roots, which can arise due to disc herniation, degeneration of intervertebral disc and narrowing of the intervertebral foramen through which the nerve roots exit (Mansfield et al. 2020).

There are multiple treatment strategies for cervical and lumbar radiculopathy, including operative and non-operative. Non-operative measures are mostly applicable in the initial stages where the pathological process can be arrested or reversed. Degeneration of intervertebral disc leads to decrease in intervertebral space, leading therefore to radicular pain. This degenerative process is thought to be due to an inflammatory process, which involves an imbalance between catabolic and anabolic signalling. Catabolic cytokine IL-1β and TNFα are key regulators of intervertebral disc degeneration (Daniels et al. 2017). IL-1 and TNF upregulate catabolic enzymes like A disintegrin and metalloproteinase with thrombospondin motifs −4,5 (ADAMTS) and matrix metalloproteases (MMPs) and decrease expression of anabolic extracellular matrix (ECM) proteins like aggrecan and collagen II, thus they cause breakdown of the ECM and they also cause the cells of the intervertebral disc

to release proinflammatory cytokines which further attract inflammatory cells, thus accelerating the process of degeneration (Johnson et al. 2015). As a result, mitigating the effect of IL-1 and TNF may emerge as a potential treatment strategy for lumbar and cervical radiculopathy.

Anakinra is an IL-1 receptor antagonist (IL-1Ra) derived through recombinant DNA technology from *Escherichia coli*, though it has been used in orthopaedics for over a decade for arthrofibrosis, persistent joint effusion, gout and osteoarthritis, but due to its short lasting action, its use has been limited (Chevalier et al. 2009; Brown et al. 2010). The recent drive in therapeutics has been towards biological and autologous products. One such novel autologous product which has recently been in use is autologous conditioned serum (ACS). Wehling et al. developed the Orthokine® technique of producing ACS, wherein 50–60 mL of venous blood is incubated for 24 h at 37 ° C with medical-grade treated glass beads; it is then centrifuged, and the serum fraction is found to be rich in IL-1Ra. This IL-1 Ra was found to be partly from the breakdown of cells and partly from de novo synthesis by monocytes. This ACS can then be used as an intra-articular injection (Wehling et al. 2007). There have been multiple studies which have shown ACS to be beneficial in equine osteoarthritis model and human knee osteoarthritis. Intra-articular injections of ACS have decreased pain and improved functional scores in patients with osteoarthritis of the knee with a side effect profile comparable to placebo (Wehling et al. 2007; Ajrawat et al. 2019). It reduces the synovial inflammation and arrests cartilage degradation in osteoarthritis (Ajrawat et al. 2019). There are few studies exploring the use of ACS in lumbar and cervical radiculopathy. The effect of ACS in osteoarthritis of the knee could be similar in the therapy of radiculopathy due to age- and inflammation-related disc degeneration. Hence, we review the few studies conducted on this subject to ascertain this potential application of ACS in the future.

4.2 Methods

4.2.1 Literature Search

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al. 2009). We searched the electronic databases including PubMed, Scopus and Embase, from the date of inception of database up to 26 September 2020, without any restriction on language. The keywords used for the search were autologous serum, "autologous conditioned serum", interleukin 1, lumbar, cervical, spin* vertebral, radicular, radiculopathy (Table 4.1).

Table 4.1 Search Methodology and the key words used in various databases

Database	Date: 26 Sep 2020	Hits
Pubmed	(((autologous serum OR "autologous conditioned serum" OR interleukin 1)) AND (Lumbar OR cervical OR spin* OR vertebral)) AND (radicular OR radiculopathy) ((("autolog"[All Fields] OR "autologeous"[All Fields] OR "autologic"[All Fields] OR "autological"[All Fields] OR "autologous"[All Fields] OR "autologously"[All Fields]) AND ("serum"[MeSH Terms] OR "serum"[All Fields] OR "serums"[All Fields] OR "serum s"[All Fields] OR "serumal"[All Fields])) OR "autologous conditioned serum"[All Fields] OR ("interleukin 1"[MeSH Terms] OR "interleukin 1"[All Fields] OR "interleukin 1"[All Fields])) AND ("lumbarised"[All Fields] OR "lumbarization"[All Fields] OR "lumbarized"[All Fields] OR "lumbars"[All Fields] OR "lumbosacral region"[MeSH Terms] OR ("lumbosacral"[All Fields] AND "region"[All Fields]) OR "lumbosacral region"[All Fields] OR "lumbar"[All Fields] OR ("cervic"[All Fields] OR "cervicals"[All Fields] OR "cervices"[All Fields] OR "neck"[MeSH Terms] OR "neck"[All Fields] OR "cervical"[All Fields] OR "uterine cervicitis"[MeSH Terms] OR ("uterine"[All Fields] AND "cervicitis"[All Fields]) OR "uterine cervicitis"[All Fields] OR "cervicitis"[All Fields]) OR "spin*"[All Fields] OR ("spine"[MeSH Terms] OR "spine"[All Fields] OR "vertebral"[All Fields] OR "vertebrals"[All Fields])) AND ("radicular"[All Fields] OR ("radiculopathy"[MeSH Terms] OR "radiculopathy"[All Fields] OR "radiculopathies"[All Fields]))	43
Scopus	(ALL (autologous AND serum OR "autologous conditioned serum" OR "interleukin 1") AND ALL (lumbar OR cervical OR spin* OR vertebral) AND ALL (radicular OR radiculopathy))	352
Embase	(autologous AND serum OR 'autologous conditioned serum' OR 'interleukin 1') AND (lumbar OR cervical OR spin* OR vertebral) AND (radicular OR radiculopathy)	81

4.2.2 Study Eligibility Criteria

The inclusion criteria included in the studies were as follows:

1. Randomised controlled trials, prospective or retrospective studies or case series that included adult patients more than 18 years with unilateral or bilateral lumbar or cervical radiculopathy.
2. The authors have reported the use of autologous conditioned serum, an interleukin 1 receptor antagonist.
3. The authors have reported one or more patient-reported outcome measures including Visual Analogue Scale for pain, Short Form of Health Survey-12 or Oswestry Disability Index.
4. A minimum clinical follow-up period of 3 months.

Exclusion criteria included abstracts, review articles, case reports, studies in animals and articles that did not report any relevant clinical data.

4.2.3 Data Extraction and Management

The study data was extracted in tabular form. Specifically, data pertaining to the these characteristics were collected: demographic details (author, country and year of publication, sample size, gender distribution, mean age group, median duration of symptoms, inclusion criteria, intervention) and outcome measures (VAS—Visual Analogue Scale, ODI—Oswestry Disability Index, SLRT—Straight Leg Raising Test, NDI—Neck Disability Index, NPDS—Neck Pain Disability Scale, PCS—Physical Component score of SF-12, MCS—Mental Component score of SF-12).

4.2.4 Methodological Quality Assessment of Included Studies

All studies were assessed to check the methodological quality of studies. Randomised studies were assessed using Jadad scale (Oremus et al. 2001). Aspects like random sequence generation, blinding of outcome assessments and other biases were assessed. Modified Jadad score greater than 4 was considered to be high-quality study. The Methodological Index for Non-randomised Studies (MINORS) was used to grade the risk of bias of non-comparative studies (Slim et al. 2003). Score of 13–15 was considered to have a low risk of bias and score of 12 or less was considered to have a high risk of bias. Each study was assessed for quality by two independent reviewers (P.S and A.G).

4.3 Results

4.3.1 Literature Search

The literature search revealed 476 articles. After removing the duplicates, 412 articles were examined by title and abstract. After exclusion by title/abstract, five articles were assessed by full text to consider for inclusion. One article included only abstract and was excluded (Moser et al. 2010). The remaining four studies were considered for the systematic review (Godek 2016; Goni et al. 2015; Ravi Kumar et al. 2015; Becker et al. 2007). The literature selection process is shown in Fig. 4.1.

4.3.2 Study Characteristics

All the studies evaluated the effect of autologous concentrated serum on radiculopathy. Out of the four studies, two were randomised controlled trials (level 1) and two studies were prospective non-comparative studies (level 4). One study compared the efficacy between ACS and methyl prednisolone (MPS) and one study compared ACS with two triamcinolone concentrations. Three studies evaluated the effect of the interleukin 1 receptor antagonist on lumbar radiculopathy while one study evaluated the effect on cervical radiculopathy. A total of 107 patients received ACS for treatment.

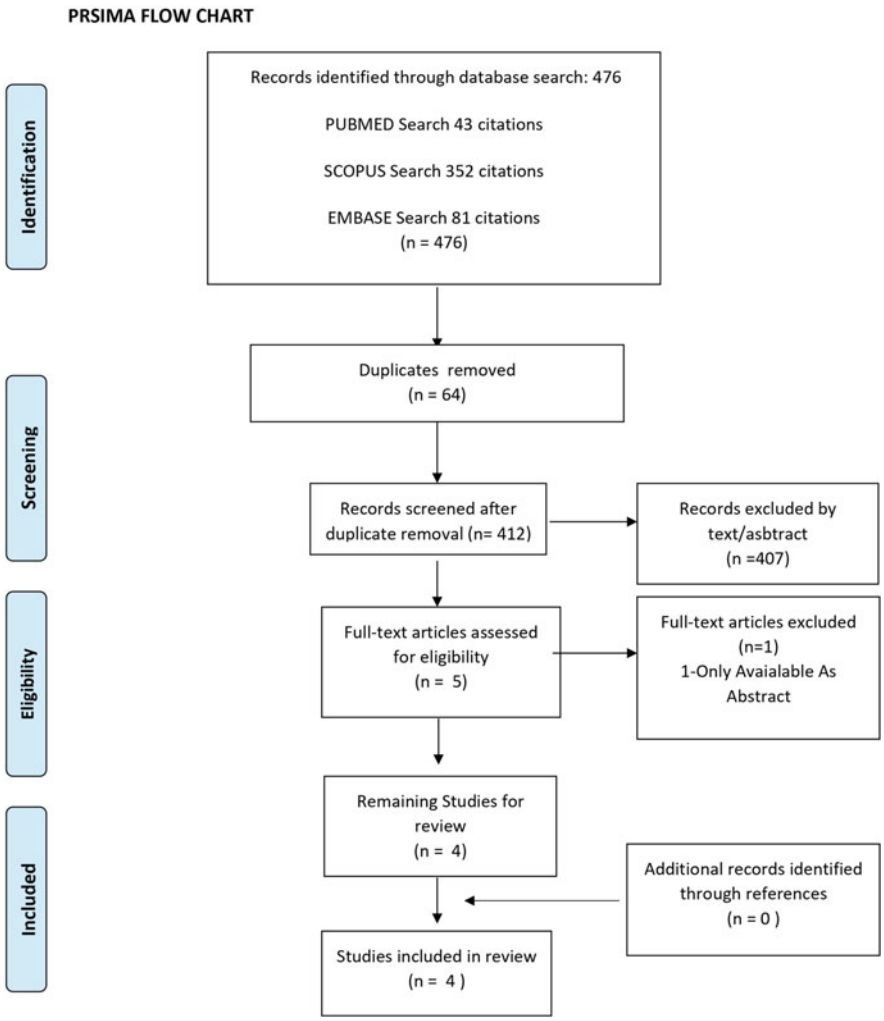

Fig. 4.1 PRISMA flow diagram for study selection

4.3.3 Demographic Variables

All the studies had a predominance of male patients, except Ravi Kumar et al. who have not detailed about gender distribution (Ravi Kumar et al. 2015). The patients were adults who had symptoms of unilateral radiculopathy for at least 6 weeks. The included patients had both clinical and radiographic signs of disc herniation in the spine causing the symptoms. The mean age of patients in the studies ranged from 37.15 to 53.9. The dose of ACS used was 2–4 mL injection of ACS (Table 4.2).

Table 4.2 Demographics and details of selected studies for the systematic review

Author	Country and year of publication	Sample size	Gender distribution	Mean age group (in years)	Median duration of symptoms	Inclusion criteria	Intervention (injection to affected intervertebral foramen)	Outcome measures	Follow-up (after first injection)
Godek et al.	Poland, 2016	15	Male: 9 (60%) Female: 6 (40%)	38.9 ± 8.9 (27–54)	16 weeks (IQ 5.5–42-2 weeks)	• Age > 18 years • Clinical + radiographic signs of single level nucleus pulposus herniation in the lumbar spine • Unilateral lumbar radiculopathy	3–4 mL injection of ACS	• VAS • ODI • One leg standing test • SLRT	• 1 month • 3 months
Goni et al.	India, 2015	40	Male: 23 (57.5%) Female: 17 (42.5%)	44.52	13.8 months (ACS 14.5 months (methylprednisolone)	• Age: 30–60 years • Unilateral cervical radiculopathy >6 weeks duration • Pain with VAS > 7/10 • Radiological and clinical signs of nerve root nerve root involvement	2–3 mL injection of • ACS (study) • Methyl prednisolone (control)	• VAS • NPDS • NDI • SF-12	• 3 weeks • 3 months • 6 months

(continued)

Table 4.2 (continued)

Author	Country and year of publication	Sample size	Gender distribution	Mean age group (in years)	Median duration of symptoms	Inclusion criteria	Intervention (injection to affected intervertebral foramen)	Outcome measures	Follow-up (after first injection)
Ravi Kumar et al.	India, 2015	20		37.15		• Age: 30–60 years • Unilateral lumbar radiculopathy >6 weeks duration • Clinical (positive SLRT) and radiological signs of lumbar nerve root involvement	2 mL injection of ACS	• VAS • ODI • SLRT • SF-12	• 3 weeks • 3 months • 6 months
Becker et al.	Germany, 2007	84	Male: 52 (61.9%) Female: 32 (28.1%)	53.9 (29–81)		• Unilateral lumbar radiculopathy • Pain >6 weeks duration • Radiology showing nucleus pulpous degeneration	• ACS • 5 mg triamcinolone • 10 mg triamcinolone	• VAS • ODI	• 6 weeks • 10 weeks • 22 weeks

ACS autologous conditioned serum, *VAS* Visual Analogue Scale, *ODI* Oswestry Disability Index, *SLRT* Straight Leg Raising Test, *NDI* Neck Disability Index, *NPDS* Neck Pain Disability Scale, *SF-12* 12 item short form survey

4.3.4 Methodological Quality Assessment

Both the RCTs were well-conducted trials and have properly described randomisation method. Overall, both the RCTs showed high methodological quality as evaluated by the Jadad scale (Oremus et al. 2001). On evaluation by the MINORS criteria, the two non-comparative prospective studies have achieved a grade of C (score of 12 or less), indicating a high risk of bias and moderate study quality. Overall the studies ranged from moderate to high quality of studies (Tables 4.3 and 4.4).

4.3.5 Medication Use and Injection Protocol

Treatment injection: The intervention included use of 2–4 mL of autologous conditioned serum. The ACS was prepared according to the technique described by Meijer et al. (2003). Godek et al. utilised ultrasound guidance as a means to inject the ACS, while the other three studies have utilised fluoroscopic imaging guidance to inject the ACS (Godek 2016). The injections were administered by epidural perineural technique in all. The injection was repeated weekly, up to a maximum of three doses overall, depending on the pain intolerance.

Control injection: One RCT divided the patients into two groups, in which a similar amount of methylprednisolone was used as control (Becker et al. 2007). In the other RCT, three groups were used in which 5 mg and 10 mg of triamcinolone were used as control (Goni et al. 2015).

4.3.6 Patient-Reported Clinical Outcomes

1. ***Visual Analogue Scale*:** All the four studies reported VAS pain as an outcome measure. Ravi et al. reported a significant change in VAS at each follow-up from pre-injection up to the third follow-up ($p < 0.001$) (Ravi Kumar et al. 2015). Godek et al. have also reported a statistically significant reduction in VAS at first and second follow-up (Godek 2016). Becker et al. found a significant change in VAS score within the treatment group from pre-injection to final follow-up ($p < 0.001$); they also found a statistically significant difference ($p = 0.046$) when compared to triamcinolone 5 mg group (but not 10 mg group) at the final follow-up (Becker et al. 2007). Goni et al. also found a good improvement of 73.2% over the baseline score in VAS at the follow-up time of 6 months (Goni et al. 2015) (Table 4.5).
2. ***Oswestry Disability Index*:** Three studies have reported Oswestry Disability Index in the patients (Godek 2016; Ravi Kumar et al. 2015; Becker et al. 2007). Ravi et al. reported the ODI score has significantly improved from pre-injection to the final follow-up ($p < 0.001$) and also in between the follow-ups ($p = 0.001$). Godek et al. reported a baseline ODI score of 39.2%, which improved to 20.9% and 14.7% at first month and third month, respectively. As per

Table 4.3 Quality assessment of the study by Modified Jadad scores

Corresponding author	Was the research described as randomised?	Was the approach of randomisation appropriate?	Was the research described as blinding?	Was the approach of blinding appropriate?	Was there a presentation of withdrawals and dropouts?	Was there a presentation of the inclusion/ exclusion criteria?	Was the approach used to assess adverse effects described?	Was the approach of statistical analysis described?	Total
Goni et al.	1	1	1	1	0	1	1	1	**7**
Becker et al.	1	1	1	0	1	1	1	1	**7**

Table 4.4 Quality assessment of the included studies by Individual MINORS score

	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to study aim	Unbiased assessment of study endpoint	Follow-up period appropriate to study aim	<5% lost to follow-up	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total
Ravi Kumar et al.	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12/16
Goni et al.	2	2	1	2	0	2	2	0	NA	NA	NA	NA	11/16

Table 4.5 Base line and follow up outcome scores of the included studies

	Baseline						
Author	VAS	ODI	PCS	MCS	SLRT	NDI	NPDS
Godek et al.	55	39.2%			60.00		
Goni et al.	• ACS-71 • MPS-69		• ACS-27.35 • MPS-28.22	• ACS-36.22 • MPS-36.53		• ACS-62.3 • MPS-64.4	• ACS-70.70 • MPS-70.05
Ravi Kumar et al.	69.5	27.9%	27.25	36.59	42.00		
Becker et al.	• ACS-78 • Triamcinolone 5 mg-82 • Triamcinolone 10 mg-85	• ACS-22% • Triamcinolone 5 mg-20.6% • Triamcinolone 10 mg-19.4%					

Follow-up						
	VAS (mean difference)			ODI/NDI		
Author	I	II	III	I	II	III
Godek et al.	44 (20%)	36(34.4%)		20.9%	14.7%	
Goni et al.	• ACS-35 • MPS-22	• ACS-24 • MPS-25.5	• ACS-19 • MPS-27.5	• NDI-ACS-35.00% • NDI-MPS-19.30%	• NDI-ACS-20.00% • NDI-MPS-25.10%	• NDI-ACS-15.9% • NDI-MPS-30.40%
Ravi Kumar et al.	36.5	22.5	20	14.95%	10.5%	8.5%
Becker et al.			• ACS-23.3±24.8 • Triamcinolone 5 mg-36.8±28.3 • Triamcinolone 10 mg-32.6±28.2	• ACS-13.8% • Triamcinolone 5 mg-12.1% • Triamcinolone 10 mg-11%	• ACS-11.2% • Triamcinolone 5 mg-12.4% • Triamcinolone 10 mg-11%	• ACS-11.7% • Triamcinolone 5 mg-11.1% • Triamcinolone 10 mg-11.4%

(continued)

Table 4.5 (continued)

Follow-up									
	SF-12 (PCS/MCS)			SLRT			NPDS		
Author	I	II	III	I	II	III	I	II	III
Godek et al.				75	77				
Goni et al.	• ACS-39.47/43.09 • MPS-48.70/45.76	• ACS-46.60/45.17 • MPS-45.90/43.16	• ACS-49.08/47.12 • MPS-44.39/42.42				• ACS-34.05 • MPS-23.85	• ACS-24.70 • MPS-27.95	• ACS-18.55 • MPS-31.1
Ravi Kumar et al.	40.08/43.46	47.59/45.79	49.32/47.51	69	74	76			
Becker et al.									

ACS Autologous conditioned serum, *VAS* Visual Analogue Scale, *ODI* Oswestry Disability Index, *SLRT* Straight Leg Raising Test, *NDI* Neck Disability Index, *NPDS* Neck Pain Disability Scale, *MPS* Methyl Prednisolone, *PCS* Physical Component score of SF-12, *MCS* Mental Component score of SF-12

Becker et al., the within-group analysis of ODI score in the ACS group improved significantly ($p < 0.001$); however, there was no statistically significant difference between the ACS group and the two triamcinolone groups.

3. ***Straight Leg Raising Test*:** Two studies have reported changes in SLRT scores (Godek 2016; Ravi Kumar et al. 2015). Ravi et al. reported a significant change from pre-injection to first, second and final follow-up ($p < 0.001$); however, the changes in between the follow-ups were not significant ($p = 0.399$ for first to second follow-up and $p = 0.115$ for second to third follow-up). Godek et al. also stated that SLR test showed a higher degree of leg raise without pain.
4. ***SF-12:*** Two studies reported PCS and MCS components of SF-12 (Goni et al. 2015; Ravi Kumar et al. 2015). Ravi et al. reported a significant difference between pre-injection and first, second and third follow-up ($p < 0.001$) and also between first and second follow-up ($p = 0.001$) and between second and third follow-up ($p = 0.001$). The MCS has also improved significantly from the pre-injection time to all the three follow-ups ($p < 0.001$); however, there was no significant change in MCS in-between the follow-ups. Goni et al. reported improvement in PCS from 27.35 (pre-injection) to 49.08 at the final follow-up, an increase of 79.45% and the MCS improved by 30.09% at the final follow-up.
5. ***Neck Pain Disability Scale and Neck Disability Index:*** Only Goni et al. reported these two outcomes as they have evaluated ACS in cervical radiculopathy (Goni et al. 2015). The mean NPDS score showed a decrease of 73.76% from the pre-injection to the final follow-up (in comparison to 55.6% in the MPS group). The NDI showed a decrease of 74.47% compared with 52.80% in the MPS group from pre-injection to the final follow-up.

4.4 Discussion

Four studies were reviewed, and all of the studies concluded that epidural perineural injection autologous conditioned serum reduced pain scores (VAS, NPDS) and improved functional scores (ODI, SF-12 and NPDS), as compared to placebo and other conventional therapeutic modalities like steroids and analgesic-anaesthetic-steroid cocktail. ACS is a rich source of autologous IL-1Ra, derived from venous blood of the patient and incubated with medical-grade glass beads for 24 h, and the IL-1Ra and other anti-inflammatory cytokines like TGF-β, FGF and PDGF are thought to be partially from cell break down and partially generated de novo from monocytes as proven by cycloheximide inhibition (Ajrawat et al. 2019). IL-1 and TNF-α are the primary inflammatory cytokines implicated in multiple inflammatory arthritis and age-related degenerative processes (Wehling et al. 2007). Targeted therapy to these cytokines may help arrest the progress of inflammation-related damage and growth factors may even aid regeneration. Therefore, ACS is a promising prospect for future use in non-operative therapy of radiculopathy. Low back ache and neck pain due to radiculopathy are some of the most common cases faced by the orthopaedic surgeons in an outpatient setting. The use of autologous IL-1Ra seems to be effective and longer lasting than synthetic IL-1Ra (Anakinra),

and more level-1 studies are needed to ascertain the efficacy and benefits. Also cost benefit analysis is needed for main stream usage.

Use of ACS in osteoarthritis of knee has already been extensively studied. Baltzer et al. compared the use of intra-articular ACS, with intra-articular hyaluronic acid and saline in 376 patients, and concluded that ACS significantly reduced Western Ontario and McMaster Universities osteoarthritis (WOMAC) index at all time intervals (3 months and 6 months) as compared to the other groups ($p < 0.001$ for all comparisons). VAS ratings were also lowest in the ACS group ($p < 0.001$) (Baltzer et al. 2009). Even at the end of 2 years, WOMAC and VAS were significantly lesser ($p < 0.001$) in the ACS group (Baltzer et al. 2009). ACS has been found to be superior to other orthobiologics in common use like platelet-rich plasma (PRP). In a study conducted of 123 women with moderate osteoarthritis, WOMAC and VAS in both groups (PRP and ACS) were comparable in patients with subclinical early synovitis at the end of 3 months. However, in patients with moderate clinically significant synovitis, ACS was found to be superior to PRP at the end of 3 months with significant improvement in WOMAC and VAS ($p < 0.001$ for both comparisons) (Shirokova et al. 2017).

ACS has also been used in muscle and ligament injuries. It has been used after anterior cruciate ligament (ACL) reconstruction to reduce bone tunnel widening. Post-operative inflammation leading to increased intra-articular IL-1β levels, which in turn increases osteoclastic activity, has been implicated in bone tunnel widening, producing less than satisfactory results. Daraboset al. conducted a study in 62 patients and found that intra-articular ACS injection significantly reduced bone tunnel widening ($p < 0.05$) and synovial IL-1β levels. The ACS group had better WOMAC scores at 1-year follow-up ($p = 0.047$) (Darabos et al. 2011).

Carpenter et al. conducted a pilot study in sportsmen with muscle strains and found that ACS injection shortened the time to recovery, showed early improvement in MRI findings and led to early return to sports (Wright-Carpenter et al. 2004a). Carpenter et al. also studied the effect of ACS on muscle regeneration in a rat muscle contusion model and found that due to high concentrations of FGF-2 and TGF β in ACS, it increased the proliferation of satellite cells; thus, ACS-treated muscles had a larger percentage of large regenerating myofibres, showing that ACS potentially aids muscle healing (Wright-Carpenter et al. 2004b).

Orthobiologics are the emerging new therapeutics, like PRP for osteoarthritis of the knee and BMP (bone morphogenetic protein) in the spinal fusion and non-unions; in a similar manner, the anti-inflammatory effects of ACS can be harnessed and further research needs to be carried out on the use of ACS in other inflammatory arthritis like rheumatoid arthritis, gout and ankylosing spondylitis and also in injury-related inflammation, where also IL-1 is a key cytokine in the inflammatory process. ACS has already been effective in multiple other orthopaedic problems, and it has been used effectively in chronic Achilles tendinopathy. It has also been effective in animal muscle contusion models (Genç et al. 2018; von Wehren et al. 2019). Surely, ACS is a promising new therapeutic modality in both lumbar and cervical radiculopathy, and further studies can strengthen the present evidence regarding its efficacy and safety profile.

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