MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2024; 30: e942044
DOI: 10.12659/MSM.942044

Received: 2023.08.14
Accepted: 2023.11.30
Available online: 2024.01.03
Published: 2024.02.26

Comparative Efficacy of Ultrasound-Guided Cervical Fascial Infiltration versus Periarticular Administration of Autologous Conditioned Serum (Orthokine) for Neck Pain: A Randomized Controlled Trial Protocol Description

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Piotr Godek
ADEF 2 Małgorzata Paprocka-Borowicz
ACDEF 2 Kuba Ptaszkowski

1 Department of Orthopedics, Sutherland Medical Center, Warsaw, Poland
2 Department of Physiotherapy, Wrocław Medical University, Wrocław, Poland

Corresponding Author: Piotr Godek, e-mail: piotrgodek.smc@gmail.com
Financial support: None declared
Conflict of interest: None declared

Background: Neck pain is a prevalent and burdensome health issue, with autologous conditioned serum (ACS), like Orthokine, being a recognized treatment for musculoskeletal conditions due to its anti-inflammatory effects. However, the optimal ACS administration method for neck pain remains unclear. The existing literature lacks robust evidence, especially for different injection techniques. This study aimed to compare ACS infiltration into cervical fascia with periarticular administration to determine if the former is as effective in alleviating neck pain, offering a novel approach to its management.

Material/Methods: Our study is designed to be a single-center, prospective, randomized trial involving 100 patients. Group A (n=50) will receive ACS through fascial infiltration at tender points under ultrasound guidance, with 4 doses administered every 3 days. Group B (n=50) will receive ACS injections in the articular column (facet joints) using the same dosing schedule. We will collect data at T0 (before therapy), T1 (6 weeks after therapy), and T2 (12 weeks after therapy), assessing outcomes with the Numerical Pain Scale (NRS), Neck Disability Index (NDI), and Dynamic Proprioception Test (DPT).

Results: Enrollment begins in August 2023, and the study is set to conclude in July 2024. If data analysis, manuscript preparation, and peer review proceed smoothly, we anticipate publishing the results in late 2024 or early 2025.

Conclusions: If fascial infiltration with ACS proves equally effective as the standard periarticular method, it offers promise for patients on long-term anticoagulant treatment. Paravertebral injections in such cases carry a significant risk of bleeding, making ACS infiltration a potentially safer alternative for managing neck pain in these individuals.

Keywords: Fascia • Inflammation • Injections • Neck Pain • Randomized Controlled Trial • Serum

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/942044

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

According to the International Association for the Study of Pain (IASP), chronic pain is characterized as persistent or recurrent pain for more than 3 months [1]. Chronic pain is operationally defined based on its frequency, requiring its presence on at least half the days throughout 3, 6, or 12 months, and is further categorized by severity as mild, bothersome, or high-impact chronic pain [2]. Chronic pain poses a substantial healthcare challenge worldwide, with a prevalence of 19% among European adults and 20.4% among adults in the United States. Its widespread impact highlights the urgent need for effective pain management strategies and research efforts to alleviate its burden on individuals and healthcare systems [3]. Longer duration of pain is associated with lack of spontaneous resolution of pain [4]. Spinal pain, particularly neck pain, is one of the most prevalent and challenging conditions affecting adults across all age groups [5].

Neck pain is not only a common ailment but is also a major global health concern that exacts a significant toll on healthcare systems. The impact of neck pain reverberates through the lives of individuals, often leading to decreased quality of life, impaired daily functioning, and substantial healthcare costs [6]. In 2017, national age-standardized point prevalence estimates of neck pain ranged from 2443.9 to 6151.2 cases per 100 000 population, with the highest in Norway at 6151.2 and Finland at 5750.3, and the lowest in Djibouti at 2443.9 and South Sudan at 2449.8 [7]. Similarly, the national age-standardized annual incidence of neck pain in the same year ranged from 599.6 to 1145 cases per 100 000 population, with the highest incidence recorded in Norway at 1145 and the lowest in Canada at 599.6 [5]. These variations underscore the challenges in understanding the epidemiology of neck pain.

Neck pain is a multi-causal phenomenon. The most common source of chronic neck pain is thought to be facet-mediated pain, either secondary to previous trauma or degenerative joint disease, followed by disc-mediated pain [8]. Mechanical-dependent causes are associated with the age-related degenerative process of the intervertebral discs (IVD), leading to instability and the proliferative degenerative changes found in facet joints, uncovertebral joints (UVJ), and anterior column [9,10]. The consequence of these changes is the narrowing of the spinal canal and intervertebral foramina, causing symptoms of radiculopathy or myelopathy, as well as axial pain originating from the facet joints, which can radiate in a non-radicular pattern. These phenomena are well documented, with numerous experiments identifying pain generators in the cervical spine and mapping pain patterns often overlapping and masking shoulder pain [11].

In postural syndromes, mechanical-dependent pain often arises due to muscle imbalances, shortened tonic muscles, fascial densifications, and trigger points resulting from non-ergonomic work positions. These factors contribute to cervical myofascial pain (MCP), which encompasses both axial and referred pain syndrome [12]. The specific system of the neck fascia, including several concentric layers, may hypothetically be the cause of 'latent' compartment syndromes due to fascial densification with venous-lymphatic outflow disorders and the entrapment of small nerve structures, especially those originating from the dorsal branches of the spinal nerve. Despite the common occurrence, MCP syndromes have been much less studied as pain generators despite histology unquestionably showing a very rich nociceptive innervation of the fascia [13].

Perhaps the underlying phenomenon of MPC syndromes is low-grade inflammation (LGI). The LGI theory assumes a local accumulation of pro-inflammatory cytokines in the connective tissue (TGF-beta, IL-1, IL-6, PGE), an imbalance towards oxidative stress, and an increase in the concentration of metalloproteinases (MMP), with the simultaneous absence of systemic features of inflammation (ESR and CRP remain normal) [14]. The clinical picture of inflammation with its typical indicators (dolor, calor, tumor, dysfunction) is very diverse. Increased concentration of pro-inflammatory cytokines causes collagen and extracellular matrix (ECM) degradation, causing increased permeability of small-diameter vessels, leading to edema in the ECM [15].

LGI promotes MMP-mediated fibrosis, while tissue acidification and sympathetic nervous system activation heighten fibroblast and myofibroblast contractility through TGF-beta. ECM edema leads to collagen fiber exposure to fluid shifts, disrupting their network structure and making them vulnerable to damage and overload (network decomposition). ECM edema also triggers excessive, disordered collagen production, contributing to fascial fibrosis, limiting capillary network formation, and hindering tissue trophic processes, including cellular migration (eg, stem cells and platelets). The consequences of fibrosis encompass fascial densification, cartilage degeneration, vessel wall fibrosis, nerve ischemia, oxidative stress, and lowered pain receptor thresholds and nociceptor irritation due to cytokines and tissue-trophic issues (eg, lactic acidosis) [16-18].

If the LGI theory is true, the tender points found in the soft tissues of the painful neck are the environment for increased cytokine penetration and all of the above-described consequences. In 2022, Parisien et al [19] found that chronic pain is closely linked to chronic, non-resolved inflammation, fulfilling a definition of LGI. They showed that resolution of chronic pain/inflammation processes is an active process that requires the transcription of many genes, which remain relatively silent in non-resolving animal models and human patients.

Local administration of gene expression modulators, such as autologous conditioned serum (ACS or Orthokine), enriched

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

with interleukin-1 receptor antagonist (IL-1Ra) via coagulation in specialized medical devices, leads to a substantial increase in IL-1Ra and various growth factors [20]. This process, mediated through receptors, can reshape tissue's metabolic and biochemical characteristics, potentially breaking the chronic cycle of pain. While data from Shirokova et al [21] and Baltzer et al [22] primarily relate to chronic osteoarthritis, they suggest the potential for transitioning away from chronicity. Given the successful record of Orthokine therapy in various conditions, including osteoarthritis, tendinopathies, enteropathies, and muscular injuries, as an effective anti-inflammatory and dechronifying agent that promotes regeneration, it was chosen for this project based on its proven efficacy and safety profile in treating neck pain, both axial and radicular [23-25].

The primary aim of this study is to determine whether the superficial application of autologous conditioned serum (ACS) on the fascial layers in the location of trigger points will be at least as effective as the classic application to the cervical facet joints or epidural perineural spaces in relieving local and referred pain in patients with chronic neck pain. By investigating the efficacy of ACS in alleviating pain in the fascial compartments, the study seeks to evaluate if this application can serve as an alternative to deep injections, which may present challenges (eg, anticoagulant use) in the treatment of neck pain. Additionally, the study aims to explore the secondary benefit of identifying the fascia as another important pain generator in the pathophysiology of chronic neck pain. Recognizing the role of fascial pain in neck pain could contribute to a better understanding of the underlying mechanisms and potentially lead to more targeted and effective treatment approaches for patients experiencing neck pain.

Material and Methods

Design and Settings

This researcher-initiated therapeutic study focusing on neck pain will be a prospective clinical trial with 2 arms, featuring control groups, randomization, and an open-label design for the intervention. The study will be conducted at the Sutherland Medical Center, Warsaw, Poland (from August 2023 to July 2024). The research protocol aligns with the ethical guidelines delineated in the Declaration of Helsinki and adheres to the principles of Good Clinical Practice. The study will involve 2 treatment arms: one group will receive cervical fascial infiltration with autologous conditioned serum (ACS), and the other group will undergo the standard periarticular administration of serum. The random allocation of participants into the treatment arms will ensure unbiased assignment. All eligible patients will receive comprehensive information about the study's objectives, procedures, potential risks, and benefits before participation. The research team will ensure the privacy and confidentiality of participants' data using anonymized identifiers in all data collection and analysis. The findings of this study will contribute to a better understanding of treatment options for neck pain, improving patient care and quality of life for individuals suffering from this condition.

Ethics

The study was approved by the Bioethics Committee of the Wroclaw Medical University, Poland (reference no. KB-81/2022, February 01, 2023) and will be performed in accordance with the Declaration of Helsinki to ensure the protection of human subjects. The trial was prospectively registered on the ISRCTN registry (ISRCTN38950110). Unique Protocol ID: SMC2023001, (submission date 16/02/2023, registration date 27/02/2023, last edited 29/03/2023). All patients enrolled in the study will be appropriately informed about the study and will be required to sign written informed consent for blood draws, ACS preparation, and injections. The patients will not receive any monetary compensation for participating in the study, nor will they be required to pay for the treatment they receive. Participation in the study is entirely voluntary and offered free of charge to the patients. The study adheres to ethical principles and guidelines, ensuring patient confidentiality, privacy, and respect for their rights throughout the research process.

Participants

We plan to enroll a cohort of 100 patients in the study. Any eligible individuals, both male and female, who are at least 18 years old and experiencing chronic neck pain attributed to degenerative or overuse causes, and who seek treatment at the study center, will be given the opportunity to participate. Inclusion in the study will be contingent upon the patients' willingness to receive injections. Exclusion criteria include pregnancy, the presence of neoplastic or systemic inflammatory diseases, injuries necessitating surgical intervention, or ongoing anticoagulant therapy that cannot be temporarily discontinued. Additional exclusion criteria encompass prior surgical procedures on the cervical spine and any mental conditions that may hinder patient cooperation with the injection procedure, such as severe injection phobia.

Interventions

Each participant in the study will provide 4 blood samples, each measuring 4×10 mL. To collect these samples, a CE-marked medical device (Orthogen Lab Services GmbH, Düsseldorf, Germany) will be utilized. This device will be properly labelled with the patient's identifying information. Following the collection of whole blood, each filled device will be placed within a controlled incubator for an extended clotting period lasting

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

9 h at 37°C. Subsequently, the device will undergo centrifugation at 3000 g for 10 min. From this process, 4 mL of serum per device will be extracted. This serum, referred to as cell-free autologous conditioned serum (ACS), contains growth factors, cytokines, and other pro-regenerative elements that are released during the extended coagulation phase. The treatment regimen will consist of 4 applications, with each involving a single 4-mL dose of ACS. These treatments will be administered at 3-day intervals by the same healthcare provider. The first treatment will occur immediately after preparation of the serum. For storage purposes, ACS will be kept frozen at -18°C or lower until subsequent treatments are administered.

The experimental group will undergo ACS (Orthokine) injections under ultrasound guidance administered in-plane into the cervical fascial planes using the hydrodissection method at tender points identified by palpation. This technique allows for a more uniform and extensive distribution of the injected material compared to conventional local soft-tissue infiltration, like prolotherapy. The hydrodissection will target the superficial fascia of the neck, nape, and suprascapular region, wherever trigger points are present. These trigger points, marked with a marker, will receive approximately 0.3-0.5 ml of serum per point, determined based on the patient's current report. The entire 4-ml volume of serum will be distributed to the deep fascia of the neck adjacent to the joint column. The needle will touch the bony base of the joint column but not enter the joint cavity, as it is not technically feasible to administer such a volume into a single joint.

The control group will receive ACS (Orthokine) injections under ultrasound guidance along the periarticular inter-articular joints of the cervical spine. In this group, all injections will be administered out-plane, with the linear probe positioned longitudinally along the articular column, aiming at the level of greatest discopathy severity (determined by the size of the herniation or the degree of narrowing in the root canal or canal itself in cases of residual disc form and dominant degenerative lesions).

Measurements

All outcomes will be measured before treatment (T0 at baseline), 6 weeks after the last injection (T1), and 12 weeks after the last injection (T2). The following outcome measures have been selected to measure efficacy: Numeric Rating Scale (NRS: score from 0 to 10), Neck Disability Index (NDI: score from 0 to 50), and Dynamic Proprioception Test (DPT: shape outline error). Three primary outcome criteria are defined and will be tested in hierarchical order: (1) Change in pain NRS from baseline to week 12 in the experimental group. (2) Change in pain NRS from baseline to week 12 in the control group. (3) Non-inferiority between groups in pain NRS from baseline to week 12. Secondary outcome measures are all other outcome measures at each of the time points listed above. Safety will be assessed using the adverse event form.

Numeric Rating Scale

The Numeric Rating Scale (NRS) is a simple and widely used tool for measuring subjective experiences, most commonly pain intensity. It provides a numerical representation of the intensity of a particular sensation or symptom experienced by an individual. The NRS is easy to administer, making it a popular choice in clinical settings, research studies, and patient self-assessments. For pain assessment, the NRS is typically presented as a horizontal or vertical line with numbers ranging from 0 to 10 (or sometimes 0 to 100). Each number on the scale corresponds to a level of pain intensity, and participants or patients are asked to choose the number that best reflects their current pain level. The scale is designed to be intuitive, allowing individuals to provide a quick and straightforward rating of their pain experience. The key points on the NRS for pain assessment are usually described as follows: 0: "No Pain" – The individual indicates that they have no pain at all; 1-3: "Mild Pain" – The pain is noticeable but generally tolerable; 4-6: "Moderate Pain" – The pain is more significant and may interfere with daily activities; 7-9: "Severe Pain" – The pain is intense and may be debilitating, significantly affecting daily life; and 10: the "Worst Possible Pain" – The individual indicates they are experiencing the most severe pain imaginable. The NRS allows for a quantitative assessment of pain intensity, where a higher number corresponds to more severe pain. This numerical representation facilitates communication between healthcare professionals and patients, making it easier to understand and track changes in pain over time or with different treatments. The versatility and ease of use make the Numeric Rating Scale a valuable tool in various medical and research settings for evaluating and monitoring various symptoms and sensations [26-28].

Neck Disability Index

The Neck Disability Index (NDI) is a validated self-report questionnaire designed to assess the impact of neck pain on an individual's functional ability and daily activities. It is commonly used as an outcome measure in clinical settings, research studies, and rehabilitation programs to evaluate the severity of neck-related disability and monitor changes in function over time. The NDI consists of 10 items, each addressing a specific aspect of functional disability related to neck pain. For each item, the individual is asked to choose 1 of 6 options that best represents their level of disability, ranging from 1 to 5: 1: No disability – The individual has no difficulty performing the activity; 2: Mild disability – The activity causes mild difficulty, but the individual can perform it independently; 3: Moderate

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

disability – The activity is somewhat difficult, and the individual may need some help or modification to perform it; 4: Severe disability – The activity is very difficult, and the individual requires significant assistance to perform it; 5: Complete disability – The individual cannot perform the activity at all. The 10 items in the NDI questionnaire cover various functional domains, including pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation. The scores for each item are summed to obtain a total score, which represents the overall level of neck disability. To calculate the NDI score, the responses from all 10 items are summed, resulting in a total score that ranges from 0 to 50 (0-4: No disability; 5-14: Mild disability; 15-24: Moderate disability; 25-34: Severe disability; 35-50: Complete disability). The total score is then multiplied by 2 to obtain a percentage, converting it to a scale ranging from 0% to 100%. A higher NDI score indicates greater neck-related disability and functional limitations. The NDI is valuable for assessing the efficiency of neck pain management, including physical therapy, medication, or other interventions, as it allows healthcare professionals to track changes in disability levels over time. Additionally, the NDI can help identify specific areas of functional limitation, guiding targeted interventions and rehabilitation strategies to improve neck pain-related disability and overall well-being [29-31].

Dynamic Proprioception Test

The Dynamic Proprioception Test (DPT), also known as the circle drawing test, is a clinical assessment used to accurately evaluate a person's ability to perceive and reproduce a specific movement using proprioceptive feedback. Proprioception refers to the body's sense of the relative position of its different parts and the effort required to move them. It is essential for coordinating movements and maintaining balance. During the test, the individual is asked to sit in a standardized seated position with an optimal tabletop height and draw the shape of a circle on a tablet. The objective is to complete the circle-drawing task within 10 s. A computer program is used to calculate the deviation from the ideal contoured shape, expressing it as a percentage of the deviation from the reference circle. The test administrator compares the drawn circle to the reference circle and evaluates the accuracy of the reproduction. Any deviations in size, shape, or smoothness of the drawn circle may indicate proprioceptive deficits. The baseline pre-therapy test (T0) will consider the best result obtained (lowest error) from the 3 trials conducted. Similarly, the best result from the 3 trials will be selected for the follow-up test (T1) scheduled 3 months after completion of the treatment (last dose). This approach serves to familiarize the patient with the test methodology while ensuring that the final measurement remains standardized and unaffected by the learning process. The test is designed to determine manual motor control and proprioceptive hand performance, with the level of deviation potentially corresponding to deep sensory impairment due to discopathy and spinal root compression. The circle-drawing test for hand proprioception is a straightforward and practical assessment that can be conducted in various clinical settings, such as physical therapy, occupational therapy, or sports medicine. It serves to identify impairments in proprioception, which can result from injuries, neurological conditions, or other issues affecting the sensory and motor pathways [32-34].

Sample Size

The trial aims to demonstrate the therapeutic non-inferiority of the experimental treatment compared to the standard of care treatment. Therefore, the sample size is calculated for the third primary outcome. The statistical assumptions are based on data from a previous study not yet published.

The following 1-sided hypotheses were formulated:

$$H_0: \mu_e - \mu_s \leq -d \text{ versus } H_1: \mu_e - \mu_s > -d,$$

where: "d" denotes the non-inferiority limit, defined as the largest clinically acceptable difference.

If there is no difference between the standard of care and the experimental treatment, then 92 patients with a 1: 1 allocation ratio (2×46) are required to be 80% confident that the lower bound of a one-sided 97.5% confidence interval will be above the non-inferiority bound of -1. A total of 100 patients will be recruited, assuming a drop-out rate of 8%.

Statistical Analysis

Statistical analyses will encompass descriptive methods, including the use of frequency tables, means, standard deviations, and effect size calculations. For inferential analyses, suitable significance tests and confidence intervals will be employed. It is important to note that missing values will not be subject to imputation. The probabilities related to continuous data will be computed utilizing two-tailed t-tests for both paired and unpaired data, as appropriate. Confidence tables will be generated through chi-squared tests. In all analyses, a global significance level of α=0.05 will be employed, with the null hypothesis positing that the mean effect equals 0.

There is no need to adjust the significance level for multiple testing for the 3 primary outcome criteria because in the primary analysis, the 3 significance tests are tested hierarchically in the a priori order specified above. When assessing secondary outcome criteria, local levels are controlled instead of the global significance level. In the assessment of non-inferiority, a margin of 25% was established for all variables, and

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

this was then compared to the lower 2.5% confidence interval of the experimental group. The statistical analysis of both primary and secondary endpoints will be conducted in accordance with the intention-to-treat (ITT) principle, and the interpretation of results will be conducted with a confirmatory approach. Safety evaluations, on the other hand, will be conducted in an exploratory manner.

Randomization and Blinding

Randomization will be carried out using computer-generated random numbers. The participants will be randomly assigned to groups in a 1: 1 ratio. A list of consecutive numbers (from 1 to 100) will be generated prior to recruitment, and each of these numbers will be assigned randomly to 1 of the 2 study groups. In this study, there is no blinding, and it is open-label for both the observer and the injector.

Stopping Rules

The observation of each patient will be completed according to the schedule, with the last study visit at the end of 12 weeks. If at least 1 of the following criteria is met, a patient's participation in the study will be terminated prematurely: (1) withdrawal of informed consent, (2) lack of medical justification for continued participation in the study, (3) premature termination of the entire study, or (4) subsequent determination that all inclusion criteria are not met and/or that all exclusion criteria are met.

The recruitment phase of the study has a planned duration of 9 months. Patients are expected to remain enrolled for 12 weeks. The entire study is considered completed when all queries from the study coordinating center have been answered by 4 weeks after the last patient visit.

Premature termination of the trial as a whole will be considered if: (1) individual protocol violations accumulate, (2) the ethical or scientific justification for the trial is compromised or no longer valid, (3) serious adverse reactions occur in a large proportion of the patient population that suggest that patient safety can no longer be guaranteed according to the risk-benefit assessment, (4) protocol violations compromise the scientific integrity of the trial with regard to the planned statistical analysis or other aspects, (5) the conditions for proper conduct of the trial are no longer met for other reasons.

Documentation and Data Management

Data will be collected using case report forms (CRFs). The investigator is responsible for the timely, accurate, complete, and legible recording of study data on the CRF and confirms the recording by signature. Source data, as defined in the ICH E6 Good Clinical Practice (GCP) Guideline, are original documents in the patient's medical record, as well as physician letters, certified copies of original records, and laboratory printouts. In addition, all patient questionnaires (self-report) are considered as source data. Study data should be collected from patient records. CRFs are checked for completeness and consistency on arrival at the trial coordinator. In case of missing data or implausible data, queries will be generated and sent to the relevant study centers. After resolving implausible entries and completing missing data, the CRF will be submitted to the appropriate Data Management Unit for data entry.

Quality Control

Quality control will be assured by the ability to monitor participating sites. A monitoring report will be prepared for each monitoring visit, documenting the study's progress and describing any problems encountered. A separate monitoring manual describes the exact nature and extent of the monitoring activities. The coordinating investigator, or an auditor designated by the coordinating investigator, is authorized to conduct audits at the trial sites and any other sites participating in the trial. The coordinating investigator has the right to inspect and review all documents that are relevant to the trial. This right also applies to the inspectors of the regulatory authority.

Results

Enrollment is planned to start in August 2023, and the study is expected to finish in July 2024. Assuming data analysis, manuscript preparation, and the peer review process proceed without significant delays, the publication of the study findings could be anticipated sometime in late 2024 or early 2025.

Discussion

Conservative treatment of neck pain, especially chronic pain, is very difficult and debatable. Despite many treatment options, we are still struggling with very limited effectiveness, and it is very difficult to come up with strong recommendations for any method.

Recommendations announced in 2021 are of only weak or moderate strength and amount to reassurance, advice, and education, manual therapy, exercise therapy, oral analgesics and topical medications, and psychological therapies. Unfortunately, biological methods such as ACS are not included in them at all [35].

The previous methods of ACS application were based on the assumption that the main generators of pain in the cervical

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

spine are degenerative damaged facet joints, IVD, and nerve structures subject to compression by proliferative changes. This required the administration of ACS in the vicinity of these structures, usually under ultrasound or fluoroscopy guidance. In prospective observational studies on small groups of patients, the effectiveness of the ACS epidural perineural application has been demonstrated [23].

In comparative studies, compared to physical methods, traction therapy, or manual therapy, significantly better results were obtained in treating cervical radiculopathy when ACS was applied perineural under ultrasound guidance [24].

Unfortunately, there is a complete lack of studies confirming the local analgesic or anti-inflammatory effect of superficial ACS administration techniques in treating neck pain. Protocols and observations of dry needling or prolotherapy outcomes can, to some extent, confirm the hypothesis about the fascial LGI involvement in the pathogenesis of neck pain. However, in those treatment options, the emphasis is on regaining ligament stability (in the broad sense, also a component of the fascia) with a reasonably low risk of adverse events [36-38].

Similar promising outcomes with a reduction of pain intensity in the Numeric Pain Score (2.8, *P*=0.002) and a decrease in the Functional Rating Index (27.3, *P*=0.004) at 24 months with a low incidence of mild adverse reactions (2 cases) were obtained using other regenerative tools like platelet rich plasma (PRP), platelet lysate (PL), and mesenchymal stromal cells (MSC) in a case series report. However, because of the very complicated methodology of injections (combined and simultaneously ligament targeted, facet joint, and epidural), extrapolation of those observations for our methodology of fascial injections with ACS should be made with caution [39].

Risk-Benefit Analysis

The outcomes should significantly impact decision-making how to modify the optimal technique of ACS application in neck pain treatment. The superficial (fascial) ultrasound-guided ACS application technique carries a much lower risk of damage to the neurovascular structures, and due to avoiding collision with the muscular layer, there is a lower risk of bleeding, especially in patients taking anticoagulants. The periarticular injection risk is moderate, but the possibility of vessel or nerve root injury should be considered with imperfect ultrasound scanning and needle guidance techniques. Hence, proving the non-inferiority of the effectiveness of the superficial approach will have clinical significance.

Limitations and Strengths

The limitation of our investigation is the lack of a placebo and a limited observation period. The strengths are randomization, fairly numerous groups for comparison study, functional test for hand function ability, and first-ever performed application of ACS according to hydrodissection technique under the ultrasound guidance. The outcomes should significantly impact decision-making on how to modify the optimal technique of ACS application in neck pain treatment, which is a possible advantage for patients. Moreover, the study explicitly uses a non-inferiority design, which aims to show that one treatment is equal to the other beyond a pre-defined margin of clinical significance. This approach is suitable when a new treatment is expected to have similar effectiveness as an existing one. By comparing 2 treatment approaches, the study seeks to identify which might offer better pain relief and overall patient satisfaction. This patient-centered approach could help tailor treatment plans to individual patient needs and preferences.

Conclusions

If the technique of fascial infiltration using ACS is shown to be equally effective compared to the standard technique of applying serum periarticular, it could offer a promising treatment option for patients undergoing chronic anticoagulant treatment. This is particularly crucial in cases with a significant risk of bleeding associated with paravertebral injections. Furthermore, identifying fascial inflammation as one of the significant pain generators beyond the facet joints could lead to a more comprehensive understanding of the pathophysiology of neck pain. Incorporating fascial infiltration with ACS into the treatment paradigm may provide a safer alternative for managing neck pain in patients with coexisting chronic anticoagulant therapy. Additionally, recognizing the role of fascial inflammation as a potential source of pain could guide the development of more targeted and effective treatment strategies to improve patient outcomes in chronic neck pain management.

Department and Institution Where Work Was Done

Sutherland Medical Center, Warsaw, Poland.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

References:

1. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003-7
2. Von Korff M, DeBar LL, Krebs EE, et al. Graded chronic pain scale revised: Mild, bothersome, and high impact chronic pain. Pain. 2020;161(3):651-61
3. Raffaeli W, Tenti M, Corraro A, et al. Chronic pain: What does it mean? A review on the use of the term chronic pain in clinical practice. J Pain Res. 2021;14:827-35
4. Wang CK, Hah JM, Carroll I. Factors contributing to pain chronicity. Curr Pain Headache Rep. 2009;13(1):7-11
5. Kazeminasab S, Nejadghaderi SA, Amiri P, et al. Neck pain: Global epidemiology, trends and risk factors. BMC Musculoskelet Disord. 2022;23(1):26
6. Shin DW, Shin JI, Koyanagi A, et al. Global, regional, and national neck pain burden in the general population, 1990-2019: An analysis of the global burden of disease study 2019. Front Neurol. 2022;13:955367
7. Safiri S, Kolahi AA, Hoy D, et al. Global, regional, and national burden of neck pain in the general population, 1990-2017: Systematic analysis of the Global Burden of Disease Study 2017. BMJ. 2020;368:m791
8. Perolat R, Kastler A, Nicot B, et al. Facet joint syndrome: From diagnosis to interventional management. Insights Imaging. 2018;9(5):773-89
9. Bashkuev M, Reitmaier S, Schmidt H. Relationship between intervertebral disc and facet joint degeneration: A probabilistic finite element model study. J Biomech. 2020;102:109518
10. Oldweiler AB, Martin JT. In vivo relationships between lumbar facet joint and intervertebral disc composition and diurnal deformation. Clin Biomech (Bristol, Avon). 2021;88:105425
11. Katsuura Y, Bruce J, Taylor S, et al. Overlapping, masquerading, and causative cervical spine and shoulder pathology: A systematic review. Global Spine J. 2020;10(2):195-208
12. Touma J, May T, Isaacson AC. Cervical myofascial pain. In: StatPearls. StatPearls Publishing; 2023. Accessed March 22, 2023. http://www.ncbi.nlm.nih.gov/books/NBK507825/
13. Kondrup F, Gaudreault N, Venne G. The deep fascia and its role in chronic pain and pathological conditions: A review. Clin Anat. 2022;35(5):649-59
14. Rider SM, Mizuno S, Kang JD. Molecular mechanisms of intervertebral disc degeneration. Spine Surg Relat Res. 2018;3(1):1-11
15. Verzella M, Affede E, Di Pietrantonio L, et al. Tissutal and fluidic aspects in osteopathic manual therapy: A narrative review. Healthcare (Basel). 2022;10(6):1014
16. Cao TV, Hicks MR, Campbell D, Standley PR. Dosed myofascial release in three-dimensional bioengineered tendons: Effects on human fibroblast hyperplasia, hypertrophy, and cytokine secretion. J Manipulative Physiol Ther. 2013;36(8):513-21
17. Antonelli M, Kushner I. It's time to redefine inflammation. FASEB J. 2017;31(5):1787-91
18. Farrell SF, de Zoete RMJ, Cabot PJ, Sterling M. Systemic inflammatory markers in neck pain: A systematic review with meta-analysis. Eur J Pain. 2020;24(9):1666-86
19. Parisien M, Lima LV, Dagostino C, et al. Acute inflammatory response via neutrophil activation protects against the development of chronic pain. Sci Transl Med. 2022;14(644):eabj9954
20. Wehling P, Moser C, Frisbie D, et al. Autologous conditioned serum in the treatment of orthopedic diseases: The orthokine therapy. BioDrugs. 2007;21(5):323-32
21. Shirokova L, Noskov S, Gorokhova V, et al. Intra-articular injections of a whole blood clot secretome, autologous conditioned serum, have superior clinical and biochemical efficacy over platelet-rich plasma and induce rejuvenation-associated changes of joint metabolism: a prospective, controlled open-label clinical study in chronic knee osteoarthritis. Rejuvenation Res. 2020;23(5):401-10
22. Baltzer AWA, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthritis Cartilage. 2009;17(2):152-60
23. Goni VG, Singh Jhala S, Gopinathan NR, et al. Efficacy of epidural perineural injection of autologous conditioned serum in unilateral cervical radiculopathy: A pilot study. Spine (Phila Pa 1976). 2015;40(16):E915-21
24. Godek P, Murawski P, Ruciński W, Guzek M. Biological, mechanical or physical? Conservative treatment of cervical radiculopathy. Ortop Traumatol Rehabil. 2020;22(6):409-19
25. Godek P, Szajkowski S, Golicki D. Evaluation of the effectiveness of orthokine therapy: Retrospective analysis of 1000 cases. Ortop Traumatol Rehabil. 2020;22(2):107-19
26. Boonstra AM, Stewart RE, Köke AJA, et al. Cut-off points for mild, moderate, and severe pain on the numeric rating scale for pain in patients with chronic musculoskeletal pain: Variability and influence of sex and catastrophizing. Front Psychol. 2016;7:1466
27. Suzuki H, Aono S, Inoue S, et al. Clinically significant changes in pain along the Pain Intensity Numerical Rating Scale in patients with chronic low back pain. PLoS One. 2020;15(3):e0229228
28. Nugent SM, Lovejoy TI, Shull S, et al. Associations of Pain Numeric Rating Scale scores collected during usual care with research administered patient reported pain outcomes. Pain Med. 2021;22(10):2235-41
29. Young BA, Walker MJ, Strunce JB, et al. Responsiveness of the Neck Disability Index in patients with mechanical neck disorders. Spine J. 2009;9(10):802-8
30. Jorritsma W, Dijkstra PU, de Vries GE, et al. Detecting relevant changes and responsiveness of Neck Pain and Disability Scale and Neck Disability Index. Eur Spine J. 2012;21(12):2550-57
31. Pontes-Silva A, Avila MA, Fidelis-de-Paula-Gomes CA, Dibai-Filho AV. The Short-Form Neck Disability index has adequate measurement properties in chronic neck pain patients. Eur Spine J. 2021;30(12):3593-99
32. Krabben T, Molier BI, Houwink A, et al. Circle drawing as evaluative movement task in stroke rehabilitation: An explorative study. J Neuroeng Rehabil. 2011;8:15
33. Quarta E, Bravi R, Minciacchi D, Cohen EJ. Circle drawing and tracing dataset for evaluation of fine motor control. Data Brief. 2021;35:106763
34. Graves JS, Ganzetti M, Dondelinger F, et al. Preliminary validity of the Draw a Shape Test for upper extremity assessment in multiple sclerosis. Ann Clin Transl Neurol. 2023;10(2):166-80
35. Corp N, Mansell G, Stynes S, et al. Evidence-based treatment recommendations for neck and low back pain across Europe: A systematic review of guidelines. Eur J Pain. 2021;25(2):275-95
36. Dagenais S, Ogunseitan O, Haldeman S, et al. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain: A survey of practitioners. Arch Phys Med Rehabil. 2006;87(7):909-13
37. Steilen D, Hauser R, Woldin B, Sawyer S. Chronic neck pain: Making the connection between capsular ligament laxity and cervical instability. Open Orthop J. 2014;8:326-45
38. Navarro-Santana MJ, Sanchez-Infante J, Fernández-de-las-Peñas C, et al. Effectiveness of dry needling for myofascial trigger points associated with neck pain symptoms: An updated systematic review and meta-analysis. J Clin Med. 2020;9(10):3300
39. Williams C, Jerome M, Fausel C, et al. Regenerative injection treatments utilizing platelet products and prolotherapy for cervical spine pain: A functional spinal unit approach. Cureus. 2021;13(10):e18608

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]