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Journal of Turkish Spinal Surgery (www.jtss.org), is the official publication of the Turkish Spinal Surgery Society. The first journal was printed on January, in 1990. It is a double-blind peer-reviewed multidisciplinary journal for the physicians who deal with spinal diseases and publishes original studies which offer significant contributions to developing of spinal knowledge. The journal publishes original scientific research articles, invited reviews and case reports accepted by the Editorial Board, in English.

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The manuscript submitted to the journal should not be previously published (except as an abstract or a preliminary report) or should not be under consideration for publication elsewhere. Every person listed as an author is expected to have been participating in the study to a significant extent. All authors should confirm that they have read the study and agreed to the submission to the Journal of Turkish Spinal Surgery for publication. This should be notified with a separate document as shown in the "Cover Letter" in the appendix. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the journal, its editors, or the publisher. The source of any financial support for the study should be clearly indicated in the Cover Letter.

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Authors should mask patients' eyes and remove patients' names from figures unless they obtain written consent to do so from the patients, and this consent should be submitted along with the manuscript.

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Authors must state all possible conflicts of interest in the manuscript, including financial, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be

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acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Conflicts of Interest and Source of Funding".

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ARTICLE WRITING

Clinically relevant scientific advances during recent years include the use of contemporary outcome measures, more sophisticated statistical approaches, and increasing use and reporting of well-formulated research plans (particularly in clinical research).

Scientific writing, no less than any other form of writing, reflects a demanding creative process, not merely an act: the process of writing changes thought. The quality of a report depends on the quality of thought in the design and the rigour of the conduct of the research. Well-posed questions or hypotheses interrelate with the design. Well-posed hypotheses imply design, and design implies the hypotheses. The effectiveness of a report relates to brevity and focus. Drawing attention to a few points will allow authors to focus on critical issues. Brevity is achieved in part by avoiding repetition (with a few exceptions to be noted), clear style, and proper grammar. Few original scientific articles need to be longer than 3000 words. Longer articles may be accepted if substantially novel methods are reported or if the article reflects a comprehensive review of the literature.

Although authors should avoid redundancy, effectively communicating critical information often requires repetition of the questions (or hypotheses/key issues) and answers. The questions should appear in the Abstract, Introduction, and Discussion, and the answers should appear in the Abstract, Results, and Discussion sections.

Although most journals publish guidelines for formatting a manuscript and many have more or less established writing styles (e.g., the American Medical Association Manual of Style), styles of writing are as numerous as authors. Journal of Turkish Spinal Surgery traditionally has used the AMA style as a general guideline. However, few scientific and medical authors have the time to learn these styles. Therefore, within the limits of proper grammar and clear, effective communication, we will allow individual styles.

Permissions: As shown in the example in the appendix (Letter of Copyright Transfer) the authors should declare in a separate statement that the study has not been previously published and is not under consideration for publication elsewhere. Also, the authors should state in the same statement that they transfer copyrights of their manuscript to our journal. Quoted material and borrowed illustrations: if the authors have used any material that had appeared in a copyrighted publication, they are expected to obtain a written permission letter, and it should be submitted along with the manuscript.

Review articles: The format for reviews substantially differ from those reporting original data. However, many of the principles noted above apply. A review still requires an Abstract, an Introduction, and a Discussion. The Introduction still requires focused issues and a rationale for the study. Authors should convey to readers the unique aspects of their reviews which distinguish them from other available material (e.g., monographs, book chapters). The main subject should be emphasized in the final paragraph of the Introduction. As for an original research article, the Introduction section of a review typically need not to be longer than four paragraphs. Longer Introductions tend to lose focus, so that the reader may not be sure what novel information will be presented. The sections after the Introduction are almost always unique to the particular review, but need to be organized in a coherent fashion. Headings (and subheadings when appropriate) should follow parallel construction and reflect analogous topics (e.g., diagnostic categories, alternative methods, alternative surgical interventions). If the reader considers only the headings, the

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logic of the review (as reflected in the Introduction) should be clear. Discussion synthesizes the reviewed literature as a whole coherently and within the context of the novel issues stated in the Introduction.

The limitations should reflect those of the literature, however, rather than a given study. Those limitations will relate to gaps in the literature that preclude more or less definitive assessment of diagnosis or selection of treatment, for example. Controversies in the literature should be briefly explored. Only by exploring limitations will the reader appropriately place the literature in perspective. Authors should end the Discussion with abstract statements similar to those which will appear at the end of the Abstract in abbreviated form.

In general, a review requires a more extensive literature review than an original research article, although this will depend on the topic. Some topics (e.g., osteoporosis) could not be comprehensively referenced, even in an entire monograph. However, authors need to ensure that a review is representative of the entire body of literature, and when that body is large, many references are required.

Original Articles: - Original articles should contain the following sections: "Title Page", "Abstract", "Keywords", "Introduction", "Materials and Methods", "Results", "Discussion", "Conclusions", and "References". "Keywords" sections should also be added if the original article is in English.

- Title (80 characters, including spaces): Just as the Abstract is important in capturing a reader's attention, so is the title. Titles rising or answering questions in a few brief words will far more likely do this than titles merely pointing to the topic. Furthermore, such titles as "Bisphosponates reduce bone loss" effectively convey the main message and readers will more likely remember them. Manuscripts that do not follow the protocol described here will be returned to the corresponding author for technical revision before undergoing peer review. All manuscripts in English, should be typed double-spaced on one side of a standard typewriter paper, leaving at least 2.5 cm. margin on all sides. All pages should be numbered beginning from the title page.

- Title page should include: a) informative title of the paper, b) complete names of each author with their institutional affiliations, c) name, address, fax and telephone number, e-mail of the corresponding author, d) address for the reprints if different from that of the corresponding author, e) ORCID numbers of the authors. It should also be stated in the title page that informed consent was obtained from patients and that the study was approved by the ethics committee.

The "Level of Evidence" should certainly be indicated in the title page (see Table-1 in the appendix). Also, the field of study should be pointed out as outlined in Table-2 (maximum three fields).

- Abstract: A150 to 250 word abstract should be included at the second page. The abstract should be written in English and for all articles. The main topics to be included in Abstract section are as follows: Background Data, Purpose, Materials- Methods, Results and Conclusion. The Abstract should be identical in meaning. Generally, an Abstract should be written after the entire manuscript is completed. The reason relates to how the process of writing changes thought and perhaps even purpose. Only after careful consideration of the data and a synthesis of the literature can author(s) write an effective abstract. Many readers now access medical and scientific information via Web-based databases rather than browsing hard copy material. Since the reader's introduction occurs through titles and abstracts, substantive titles and abstracts more effectively capture a reader's attention regardless of the method of access. Whether reader will examine an entire article often will depend on an abstract with compelling information. A compelling Abstract contains the questions or purposes, the methods, the results (most often quantitative data), and the conclusions. Each of these may be conveyed in one or two statements. Comments such as "this report describes…" convey little useful information.

-Keywords : Standard wording used in scientific indexes and search engines should be preferred. The minimum number for keywords is three and the maximum is five.

- Introduction (250 – 750 words): It should contain information on historical literature data on the relevant issue; the problem should be defined; and the objective of the study along with the problem-solving methods should be mentioned.

Most studies, however, are published to: (1) report entirely novel findings (frequently case reports, but sometimes substantive basic or clinical studies); (2) confirm previously reported work (eg, case reports, small preliminary series) when such confirmation remains questionable; and (3) introduce or address controversies in the literature when data and/or conclusions conflict. Apart from reviews and other special articles, one of these three purposes generally should be apparent (and often explicit) in the Introduction.

INSTRUCTIONS to AUTHORS

The first paragraph should introduce the general topic or problem and emphasize its importance, a second and perhaps a third paragraph should provide the rationale of the study, and a final paragraph should state the questions, hypotheses, or purposes.

One may think of formulating rationale and hypotheses as Aristotelian logic (a modal syllogism) taking the form: If A, B, and C, then D, E, or F. The premises A, B, and C, reflect accepted facts, whereas D, E, or F reflect logical outcomes or predictions. The premises best come from published data, but when data are not available, published observations (typically qualitative), logical arguments or consensus of opinion can be used. The strength of these premises is roughly in descending order from data to observations or argument to opinion. D, E, or F reflects logical consequences. For any set of observations, any number of explanations (D, E, or F) logically follows. Therefore, when formulating hypotheses (explanations), researchers designing experiments and reporting results should not rely on a single explanation.

With the rare exception of truly novel material, when establishing rationale authors should generously reference representative (although not necessarily exhaustive) literature. This rationale establishes the novelty and validity of the questions and places it within the body of literature. Writers should merely state the premises with relevant citations (superscripted) and avoid describing cited works and authors` names. The exceptions to this approach include a description of past methods when essential to developing rationale for a new method, or a mention of authors` names when important to establish historical precedent. Amplification of the citations may follow in the Discussion when appropriate. In establishing a rationale, new interventions of any sort are intended to solve certain problems. For example, new implants (unless conceptually novel) typically will be designed according to certain criteria to eliminate problems with previous implants. If the purpose is to report a new treatment, the premises of the study should include those explicitly stated problems (with quantitative frequencies when possible), and they should be referenced generously.

The final paragraph logically flows from the earlier ones, and should explicitly state the questions or hypotheses to be addressed in terms of the study (independent, dependent) variables. Any issue not posed in terms of study variables cannot be addressed meaningfully. Focus of the report relates to focus of these questions, and the report should avoid questions for which answers are well described in the literature (e.g., dislocation rates for an implant designed to minimize stress shielding). Only if there are new and unexpected information should data be reported apart from that essential to answer the stated questions.

- Materials - Methods (1000-1500 words): Epidemiological/ demographic data regarding the study subjects; clinical and radiological investigations; surgical technique applied; evaluation methods; and statistical analyses should be described in detail.

In principle, the Materials and Methods should contain adequate detail for another investigator to replicate the study. In practice, such detail is neither practical nor desirable because many methods will have been published previously (and in greater detail), and because long descriptions make reading difficult. Nonetheless, the Materials and Methods section typically will be the longest section. When reporting clinical studies, authors must state approval of the institutional review board or ethics committees according to the laws and regulations of their countries. Informed consent must be stated where appropriate. Such approval should be stated in the first paragraph of Materials and Methods. At the outset, the reader should grasp the basic study design. Authors should only briefly describe and reference previously reported methods. When authors modify those methods, the modifications require additional description.

In clinical studies, the patient population and demographics should be outlined at the outset. Clinical reports must state inclusion and exclusion criteria and whether the series is consecutive or selected; if selected, criteria for selection should be stated. The reader should understand from this description all potential sources of bias such as referral, diagnosis, exclusion, recall, or treatment bias. Given the expense and effort for substantial prospective studies, it is not surprising that most published clinical studies are retrospective.

Such studies often are criticized unfairly for being retrospective, but that does not negate the validity or value of a study. Carefully designed retrospective studies provide most of the information available to clinicians. However, authors should describe potential problems such as loss to follow-up, difficulty in matching, missing data, and the various forms of bias more common with retrospective studies.

If authors use statistical analysis, a paragraph should appear at the end of Materials and Methods stating all statistical tests used. When multiple tests are used, authors should state which

tests are used for which sets of data. All statistical tests are associated with assumptions, and when it is not obvious the data would meet those assumptions, the authors either should provide the supporting data (e.g., data are normally distributed, variances in gro-ups are similar) or use alternative tests. Choice of level of significance should be justified. Although it is common to choose a level of alpha of 0.05 and a beta of 0.80, these levels are somewhat arbitrary and not always appropriate. In the case where the implications of an error are very serious (e.g., missing the diagnosis of cancer), different alpha and beta levels might be chosen in the study design to assess clinical or biological significance.

- Results (250-750 words): "Results" section should be written in an explicit manner, and the details should be described in the tables. The results section can be divided into sub-sections for a more clear understanding.

If the questions or issues are adequately focused in the Introduction section, the Results section needs not to belong. Generally, one may need a paragraph or two to persuade the reader of the validity of the methods, one paragraph addressing each explicitly raised question or hypothesis, and finally, any paragraphs to report new and unexpected findings. The first (topic) sentence of each paragraph should state the point or answer the question. When the reader considers only the first sentence in each paragraph in Results, the logic of the authors` interpretations should be clear. Parenthetic reference to all figures and tables forces the author to textually state the interpretation of the data; the important material is the authors` interpretation of the data, not the data.

Statistical reporting of data deserves special consideration. Stating some outcome is increased or decreased(or greater or lesser) and parenthetically stating the p (or other statistical) value immediately after the comparative terms more effectively conveys information than stating something is or is not statistically significantly different from something else (different in what way? the reader may ask). Additionally, avoiding the terms 'statistically different' or 'significantly different' lets the reader determine whether they will consider the statistical value biologically or clinically significant, regardless of statistical significance.

Although a matter of philosophy and style, actual p values convey more information than stating a value less than some preset level. Furthermore, as Motulsky notes, "When you read that a result is not significant, don't stop thinking... First, look at the confidence interval... Second, ask about the power of the study to find a significant difference if it were there." This approach will give the reader a much greater sense of biological or clinical significance.

- Discussion (750 - 1250 words): The Discussion section should contain specific elements: a restatement of the problem or question, an exploration of limitations and as-sumptions, a comparison and/or contrast with information (data, opinion) in the literature, and a synthesis of the comparison and the author's new data to arrive at conclusions. The restatement of the problem or questions should only be a brief emphasis. Exploration of assumptions and limitations are preferred to be next rather than at the end of the manuscript because the interpretation of what will follow depends on these limitations. Failure to explore limitations suggests the author(s) either do not know or choose to ignore them, potentially misleading the reader. Exploration of these limitations should be brief, but all critical issues must be discussed, and the reader should be persuaded they do not jeopardize the conclusions.

Next, the authors should compare and/or contrast their data with data reported in the literature. Generally, many of these reports will include those cited as a rationale in the Introduction. Because of the peculiarities of a given study the data or observations might not be strictly comparable to that in the literature, it is unusual that the literature (including that cited in the Introduction as rationale) would not contain at least trends. Quantitative comparisons most effectively persuade the reader that the data in the study are "in the ballpark," and tables or figures efficiently convey that information. Discrepancies should be stated and explained when possible; when an explanation of a discrepancy is not clear that also should be stated. Conclusions based solely on data in the paper seldom are warranted because the literature almost always contains previous information.

Finally, the author(s) should interpret their data in light of the literature. No critical data should be overlooked because contrary data might effectively refute an argument. That is, the final conclusions must be consistent not only with the new data presented, but also that in the literature.

- Conclusion: The conclusions and recommendations by the authors should be described briefly. Sentences containing personal opinions or hypotheses that are not based on the scientific data obtained from the study should be avoided.

- References: References are numbered (Arabic numerals) consecutively in the order in which they appear in the text (note

INSTRUCTIONS to AUTHORS

that references should not appear in the abstract) and listed double-spaced at the end of the manuscript. The preferred method for identifying citations in the text is using within parentheses. Use the form of the "Uniform Requirements for Manuscripts" (http://www.icmje.org/about-icmje/faqs/icmje-recommendations/). If the number of authors exceeds seven, list first 6 authors followed by et al.

Use references found published in peer-reviewed publications that are generally accessible. Unpublished data, personal communications, statistical programs, papers presented at meetings and symposia, abstracts, letters, and manuscripts submitted for publication cannot be listed in the references. Papers accepted by peer-reviewed publications but not yet published ("in press") are not acceptable as references.

Journal titles should conform to the abbreviations used in "Cumulated Index Medicus".

Please note the following examples of journal, book and other reference styles:

Journal article:

Berk H, Akçalı Ö, Kıter E, Alıcı E. Does anterior spinal instrument rotation cause rethrolisthesis of the lower instrumented vertebra? J Turk Spinal Surg. 1997;8:5-9.

Book chapter:

Wedge IH, Kirkaldy-Willis WH, Kinnard P. Lumbar spinal stenosis. Chapter 5. In: Helfet A, Grubel DM (Eds.). Disorders of the Lumbar Spine. JB Lippincott, Philadelphia 1978;pp:61-8.

Entire book:

Paul LW, Juhl IH (Eds). The Essentials of Roentgen Interpretation. Second Edition, Harper and Row, New York 1965;pp:294-311.

Book with volume number:

Stauffer ES, Kaufer H, Kling THF. Fractures and dislocations of the spine. In: Rock-wood CA, Green DP (Eds.). Fractures in Adults. Vol. 2, JB Lippincott, Philadelphia 1984;pp:987-1092.

Journal article in press:

Arslantaş A, Durmaz R, Coşan E, Tel E. Aneurysmal bone cysts of the cervical spine. J Turk Spinal Surg. (In press).

Book in press :

Condon RH. Modalities in the treatment of acute and chronic low back pain. In: Finnison BE (Ed.). Low Back Pain. JB Lippincott (In press).

Symposium:

Raycroft IF, Curtis BH. Spinal curvature in myelomeningocele: natural history and etiology. Proceedings of the American Academy of Orthopaedic Surgeons Symposium on Myelomeningocele, Hartford, Connecticut, November 1970, CV Mosby, St. Louis 1972;pp:186-201.

Papers presented at the meeting:

Rhoton AL. Microsurgery of the Arnold-Chiari malformation with and without hydromyelia in adults. Presented at the Annual Meeting of the American Association of Neuro-logical Surgeons, Miami, Florida, April 7, 1975.

-Tables: They should be numbered consecutively in the text with Arabic numbers. Each table with its number and title should be typed on a separate sheet of paper. Each table must be able to stand alone; all necessary information must be contained in the caption and the table itself so that it can be understood independent from the text. Information should be presented explicitly in "Tables" so that the reader can obtain a clear idea about its content. Information presented in "Tables" should not be repeated within the text. If possible, information in "Tables" should contain statistical means, standard deviations, and t and p values for possibility. Abbreviations used in the table should be explained as a footnote.

Tables should complement not duplicate material in the text. They compactly present information, which would be difficult to describe in text form. (Material which may be succinctly described in text should rarely be placed in tables or figures.) Clinical studies for example, often contain complementary tables of demographic data, which although important for interpreting the results, are not critical for the questions raised in the paper. Well focused papers contain only one or two tables or figures for every question or hypothesis explicitly posed in the Introduction section. Additional material may be used for unexpected results. Well-constructed tables are self-explanatory and require only a title. Every column contains a header with units when appropriate.

- Figures: All figures should be numbered consecutively throughout the text. Each figure should have a label pasted on its back indicating the number of the figure, an arrow to show the top edge of the figure and the name of the first author. Black-and-white illustrations should be in the form of glossy prints (9x13 cm). The letter size on the figure should be large enough to be readable after the figure is reduced to its actual printing size. Unprofessional typewritten characters are not

accepted. Legends to figures should be written on a separate sheet of paper after the references.

The journal accepts color figures for publication if they enhance the article. Authors who submit color figures will receive an estimate of the cost for color reproduction. If they decide not to pay for color reproduction, they can request that the figures be converted to black and white at no charge. For studies submitted by electronic means, the figures should be in jpeg and tiff formats with a resolution greater than 300 dpi. Figures should be numbered and must be cited in the text.

- Style: For manuscript style, American Medical Association Manual of Style (9th edition). Stedman's Medical Dictionary (27th edition) and Merriam Webster's Collegiate Dictionary (10th edition) should be used as standard references. The drugs and therapeutic agents must be referred by their accepted generic or chemical names, without abbreviations. Code numbers must be used only when a generic name is not yet available. In that case, the chemical name and a figure giving the chemical structure of the drug should be given. The trade names of drugs should be capitalized and placed in parentheses after the generic names. To comply with trademark law, the name and location (city and state/country) of the manufacturer of any drug, supply, or equipment mentioned in the manuscript should be included. The metric system must be used to express the units of measure and degrees Celsius to express temperatures, and SI units rather than conventional units should be preferred.

The abbreviations should be defined when they first appear in the text and in each table and figure. If a brand name is cited, the manufacturer's name and address (city and state/country) must be supplied.

The address, "Council of Biology Editors Style Guide" (Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) can be consulted for the standard list of abbreviations.

-Acknowledgments: Note any non-financial acknowledgments. Begin with, "The Authors wish to thank..." All forms of support, including pharmaceutical industry support should also be stated in the Acknowledgments section.

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- **Practical Tips:**

1. Read only the first sentence in each paragraph throughout the text to ascertain whether those statements contain all critical material and the logical flow is clear.

2. Avoid in the Abstract comments such as, "... this report describes..." Such statements convey no substantive information for the reader.

3. Avoid references and statistical values in the Abstract.

4. Avoid using the names of cited authors except to establish a historical precedent. Instead, indicate the point in the manuscript by providing citation by superscribing.

5. Avoid in the final paragraph of the Introduction purposes such as, "... we report our data..." Such statements fail to focus the reader's (and author's!) attention on the critical issues (and do not mention study variables).

6. Parenthetically refer to tables and figures and avoid statements in which a table of the figure is either subject or object of a sentence. Parenthetic reference places interpretation of the information in the table or figure and not the table or figure.

7. Regularly count words from the Introduction through Discussion.

TABLE-1. LEVELS OF EVIDENCE

LEVEL- I .

1) Randomized, double-blind, controlled trials for which tests of statistical significance have been performed

2) Prospective clinical trials comparing criteria for diagnosis, treatment and prognosis with tests of statistical significance where compliance rate to study exceeds 80%

3) Prospective clinical trials where tests of statistical significance for consecutive subjects are based on predefined criteria and a comparison with universal (gold standard) reference is performed

4) Systematic meta-analyses which compare two or more studies with Level I evidence using pre-defined methods and statistical comparisons.

5) Multi-center, randomized, prospective studies

INSTRUCTIONS to AUTHORS

LEVEL –II.

1) Randomized, prospective studies where compliance rate is less than 80%

2) All Level-I studies with no randomization

3) Randomized retrospective clinical studies

4) Meta-analysis of Level-II studies

LEVEL– III.

1) Level-II studies with no randomization (prospective clinical studies etc.)

2) Clinical studies comparing non-consecutive cases (without a consistent reference range)

3) Meta-analysis of Level III studies

LEVEL- IV.

1) Case presentations

2) Case series with weak reference range and with no statistical tests of significance

LEVEL – V.

1) Expert opinion and review articles

2) Anecdotal reports of personal experience regarding a study, with no scientific basis

TABLE-2. CLINICAL AREAS

Anatomy

1. Morphometric analysis

Anesthesiology

Animal study

Basic Science

1. Biology
2. Biochemistry
3. Biomaterials
4. Bone mechanics
5. Bone regeneration
6. Bone graft
7. Bone graft substitutes
8. Drugs

Disc

1. Disc Degeneration
2. Herniated Disc
3. Disc Pathology
4. Disc Replacement
5. IDET

Disease/Disorder

1. Congenital
2. Genetics
3. Degenerative disease
4. Destructive (Spinal Tumors)
5. Metabolic bone disease
6. Rheumatologic

Biomechanics Cervical Spine

1. Cervical myelopathy
2. Cervical reconstruction
3. Cervical disc disease
4. Cervical Trauma
5. Degenerative disease

Complications

1. Early
2. Late
3. Postoperative

Deformity

1. Adolescent idiopathic scoliosis
2. Kyphosis
3. Congenital spine
4. Degenerative spine conditions

Diagnostics

1. Radiology
2. MRI
3. CT scan
4. Others

INSTRUCTIONS to AUTHORS

Epidemiology

Etiology

Examination

Experimental study

Fusion

1. Anterior
2. Posterior
3. Combined
4. With instrumentation

Infection of the spine

1. Postoperative
2. Rare infections
3. Spondylitis
4. Spondylodiscitis
5. Tuberculosis

Instrumentation

Meta-Analysis

Osteoporosis

1. Bone density
2. Fractures
3. Kyphoplasty
4. Medical Treatment
5. Surgical Treatment

Outcomes

1. Conservative care
2. Patient Care
3. Primary care
4. Quality of life research
5. Surgical

Pain

1. Chronic pain
2. Discogenic pain
3. Injections
4. Low back pain
5. Management of pain
6. Postoperative pain
7. Pain measurement

Physical Therapy

1. Motion Analysis
2. Manipulation
3. Non-Operative Treatment

Surgery

1. Minimal invasive
2. Others
3. Reconstructive surgery

Thoracic Spine

Thoracolumbar Spine

Lumbar Spine

Lumbosacral Spine

Psychology

Trauma

1. Fractures
2. Dislocations

Spinal cord

1. Spinal Cord Injury

Spinal stenosis

1. Cervical
2. Lumbar
3. Lumbosacral

Tumors

1. Metastatic tumors
2. Primary benign tumors
3. Primary malign tumors

INSTRUCTIONS to AUTHORS

APPLICATION LETTER EXAMPLE:

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JOURNAL OF TURKISH SPINAL SURGERY

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JOURNAL OF TURKISH SPINAL SURGERY

EDITORIAL

Dear Colleagues,

First, I want to wish all of you and your families a very happy, peaceful, and bountiful new year. Once again, I am fortunate to be the person responsible for publishing this, the 1st issue, of our professional journal of the year. I hope that everyone will take time to examine it, and to incorporate the information in it, into your practices.

The Journal of Turkish Spinal Surgery (www.jtss.org), is the official publication of the Turkish Spine Society. JTSS is indexed in nine indices; Scopus, Ulakbim, Türkiye Atıf Dizini, Index Copernicus, J-Gate, Europub, Proquest, Gale Cengage learning and Ebsco Host.

In this issue, there are six clinical research studies, and one basic science study. The authors in the first study examined the "Relationship Between Myofascial Pain Syndrome and Coronal and Sagittal Alignment in Adolescent Idiopathic Scoliosis". The second is a study about the "Treatment Options and Surgical Indications in Spinal Metastasis Cases: Sins and Noms Classifications." In the third, one can read about the "Relationship Between Facet Tropism, Lumbar Degeneration and Facet Degeneration." The authors of the fourth article wrote about the fact that "Ultrasonography in Caudal Injections Can Reduce the Use of Fluoroscopy." The authors of the fifth study reported about the "Effect of Rigid and Hybrid Rod on the Development of Adjacent Segment Disease After Lumbar Spinal Fusion." The sixth study is a retrospective observational study of "Paravertebral Intramuscular Ozone/oxygen Injection in the Treatment of Chronic Nonspecific Low Back Pain" while, in the seventh, the authors wrote about the "Effect of Mesenchymal Stem Cell and Erythropoietin Combination in a Rat Spinal Fusion Model."

As always, I hope you felt this issue was invigorating and enlightening. My goal continues to be to bring you the most current information in our field in order to keep us on the forefront of the latest research and developments.

Once again, I wish all of our Turkish spinal surgeons and their families a healthy, peaceful, and prosperous 2023.

With kindest regards,

Editor in Chief

Metin Özalay, M.D.

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DOI: 10.4274/jtss.galenos.2022.18480

ORIGINAL ARTICLE
1

IS THERE A RELATIONSHIP BETWEEN MYOFASCIAL PAIN SYNDROME AND CORONAL AND SAGITTAL ALIGNMENT IN ADOLESCENT IDIOPATHIC SCOLIOSIS?

Merve Damla Korkmaz[1], Murat Korkmaz[2], Yekta Furkan Altın[2], Turgut Akgül[2]

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ABSTRACT

Objective: To investigate the presence of myofascial pain syndrome (MPS) in adolescent idiopathic scoliosis (AIS) and the relationship between the presence of MPS and coronal/sagittal alignment in participants with AIS.

Materials and Methods: This was a prospective, cross-sectional study. Participants with AIS aged 10-18 years were included in the study and separated into two groups according to having MPS: AIS with MPS group and AIS without pain (non-MPS group). Participants' demographic characteristics, Cobb angle, coronal balance, the presence of MPS, the location of the curve and pain, sagittal spinopelvic parameters [sagittal vertical axis, cervical lordosis (CL), thoracic kyphosis (TK), lumbar lordosis (LL), pelvic tilt, sacral slope, pelvic incidence], aesthetic evaluation, and visual analog scale results were evaluated and both groups were compared in terms of these parameters.

Results: One hundred sixty eight participants diagnosed with AIS aged 10-18 years were included in the study. The mean age was 14.9±2.2 years. Participants were separated into two groups:the MPS group (n=106) and non-MPS group (n=62). The location of myofascial pain was more common in the lumbar (23.8%) and main thoracic regions (23.2%) in participants diagnosed with MPS. Age, Cobb angle, CL, TK, LL, and Trunk Aesthetic Clinical Evaluation tool (p=0.001, 0.018, 0.016, 0.024, 0.011, and 0.031, respectively) were found significantly different between both groups. Also, decreased CL angle (odds ratio=0.960) was determined as a significant risk factor for the presence of MPS. There was no relationship between pain intensity and the location of the major curve or the location of the pain.

Conclusion: MPS should be remembered as a source of pain in AIS. Older age, greater curve size, decreased CL, increased TK and LL angles, and the worst aesthetic appearance was found in participants with AIS and MPS. The location of myofascial pain or the location of the major curve was not associated with pain intensity.

Keywords: Aesthetics, myofascial pain, sagittal alignment, scoliosis, trigger point

INTRODUCTION

Back pain is one of the common complaints in adolescent idiopathic scoliosis (AIS)[1-3]. There are so many reasons for back pain in the pediatric population: Spondylolysis and spondylolisthesis, trauma and degenerative conditions, infectious and inflammatory diseases, neoplasms, myofascial problems, etc. As we know, spinal asymmetry is accepted as a risk factor for the presence of back pain in scoliosis[4]. Also, the spinal deformity may deteriorate the biomechanics of the spine and paraspinal muscles and can cause increased inflammatory responses[5]. The prevalence of back pain in AIS was found to be between 23% and 85%, and it was reported that patients with AIS had a higher prevalence of back pain than patients without scoliosis[3,5].

The mechanism of the myofascial pain syndrome (MPS) is still controversial. Alterations of inflammatory markers in circulation have been investigated for MPS, and elevated inflammatory biomarkers (C-reactive protein, IL-6, IL-1β, etc.) were observed in patients with myofascial pain[6]. Additionally, mechanical factors such as prolonged abnormal posture have been recognized as a risk factors for MPS[7-9]. Scoliosis is one of the precipitating structural reasons for the MPS[10]. According to a review article by López-Torres et al.[11], muscular imbalance in scoliosis can also cause pain, and myofascial release techniques and postural control have been found useful for this myofascial pain in scoliosis.

As far as we know, there is no literature on MPS and scoliosis. Based on this information, it was aimed to investigate the presence of MPS in AIS, and to determine the relationship between sagittal and coronal alignment and MPS in participants with AIS.

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MATERIALS AND METHODS

It was a prospective, cross-sectional trial. Participants who were admitted to Scoliosis Outpatient Clinic in University of Health Sciences Turkey, İstanbul Kanuni Sultan Süleyman Training and Research Hospital were evaluated for eligibility, and those who met the inclusion criteria were included in the study between October 10, 2021, and April 25, 2022. The inclusion criteria were being diagnosed with AIS, being between the ages of 10-18 years, agreeing to participate in the study, and for the MPS group, meeting the diagnostic criteria for active trigger points (TrPs)[12]: A palpable taut band in the muscle, local twitch response, a hypersensitive tender spot in the taut band, and referred pain pattern. Having neurological deficits or other pathologies for secondary scoliosis, having other causes for pain except for the MPS (discopathy, spondylolysis, spondylolisthesis, etc.), receiving brace or exercise therapy for scoliosis, having a history of spinal trauma, and the previous history of the spinal surgery was accepted as the exclusion criteria.
Participants were separated into two groups according to the presence of myofascial pain: AIS with MPS (MPS group) and AIS without pain (non-MPS group).

Ethical Status

The study protocol was approved by the University of Health Sciences Turkey, İstanbul Kanuni Sultan Süleyman Training and Research Hospital Ethical Board in conformity with the Declaration of Helsinki (under number: KAEK/2020.07.128). Written and verbal consent forms were obtained from the participants. Also, the study was registered at Clinicaltrials.gov (ID No: NCT05185050).

Outcome Measures

The characteristics of the participants were recorded at first applying to the scoliosis outpatient clinic. The clinical evaluation was performed by an investigator, and all radiographic parameters were measured using the Surgimap® software program by another investigator.

Scoliosis Severity and Location of the Curve

Cobb angle was measured to determine the scoliosis severity[1]. The location of the major curve was specified according to the Lenke classification (proximal thoracic, main thoracic, thoracolumbar, and lumbar)[13].

Spinal Coronal Balance

The horizontal distance between the vertical line drawn from the center of the C7 vertebra and the vertical line drawn from the center of S1 was measured for coronal balance[14].

Spino-pelvic Sagittal Balance

The sagittal vertical axis (SVA), cervical lordosis (CL), thoracic kyphosis (TK), and lumbar lordosis (LL) angles were measured for evaluating sagittal spinal balance, and pelvic tilt (PT), sacral slope (SS), and pelvic incidence (PI), were measured for evaluating sagittal pelvic balance[15].

Aesthetic Evaluation

The Trunk Aesthetic Clinical Evaluation (TRACE) tool was used for the aesthetic examination of the participants. It is a 12-point scale that evaluates shoulder, hemithorax, scapulae, and waist asymmetries[16].

Presence of MPS and Pain Intensity

The diagnosis of MPS was made according to the diagnostic criteria of Simon et al[17]. According to these criteria, at least one minor criterion and five major criteria were needed for diagnosis. The major criteria were (i) spontaneous localized pain, (ii) referred pain from the TrPs, (iii) palpable taut band in the muscle, (iv) localized tenderness in a taut band, and (v) decreased range of motion. The minor criteria were (i) altered sensations by pressure on the TrPs, (ii) local twitch response by transverse snapping palpation or needling of a TrPs, (iii) reducing pain by stretching of the muscle or TrP injections[12,17]. Pain intensity was evaluated using visual analog scale (VAS). There is a 10 cm horizontal line on the scale from "no pain" to "very severe pain"[18]. The location of the pain was classified as cervical/proximal thoracic (TrPs in the trapezius muscle were also assumed to be in this group), main thoracic, thoracolumbar, and lumbar regions according to palpation of the TrPs.

Calculation of the Sample Size

It was calculated with the G*power program. Based on the mean value of Cobb angle to achieve $\alpha<0.05$ and $\beta=95\%$, a minimum of 62 participants were calculated for each group as described by Teles et al.[19].

Statistical Analysis

All the analyses of the data were performed with SPSS® (MacOs, IBM Corp., Armonk, NY, USA) v23.0. The distribution of the variables was assessed by histogram and Shapiro-Wilk test. Characteristics of the participants were defined as mean (standard deviation), median (minimum-maximum), and percentages. Inter-group analysis was performed with an independent t-test or Mann-Whitney U test based on the distribution of the variables, and chi-square (χ^2) test was performed for categorical variables. After the screening of the independent variables with univariate analysis, multiple regression analysis was performed. All results were evaluated in the 95% confidence interval and $p<0.05$ was considered statistically significant.

RESULTS

Two hundred and ninety-six children with scoliosis were evaluated for eligibility. One hundred and sixty-eight participants diagnosed with AIS aged 10-18 years were included in the study. One hundred and twenty-eight participants have excluded: Twenty-four participants had neuromuscular scoliosis, twenty-two of them were not between the ages of 10-18 years, thirty-six of them were currently receiving brace and/or exercise therapy, eight had a previous history of spinal surgery,

nine were diagnosed with spondylolisthesis, three of them were diagnosed with spondylolysis, and two were diagnosed with lumbar discopathy, twenty-two participants only had a local muscle spasm without referred pain or local twitch response, and two had a history of spinal trauma (Figure 1).

Participants were divided into two groups according to the presence of MPS: The MPS group (n=106) and the non-MPS group (n=62). The mean age of the participants was 14.9±2.2 years. They were homogeneously distributed in both groups in terms of age, gender, Risser classification, Tanner stage, and location of the major curve. The location of pain was more common in the lumbar (23.8%) and main thoracic regions (23.2%) in participants diagnosed with MPS (Table 1).

Based on the comparison of the MPS and non-MPS groups for spinal coronal/sagittal alignment and aesthetic evaluation, there were statistically differences in terms of age, Cobb angle, CL angle, TK angle, LL angle, and TRACE tool (p=0.001, 0.018, 0.016, 0.024, 0.011, and 0.031, respectively). No significant difference was shown in terms of coronal balance, PT, SS, PI, and SVA (Table 2). Those variables with p<0.20 in univariate analysis were included in the logistic regression analysis. Based on the results, decreased CL angle (odds ratio: 0.960) was determined as a significant risk factor for the presence of MPS in AIS (Table 3).

When the MPS group was divided into three groups mild (VAS: 1-4), moderate (VAS: 5-6), and severe pain (VAS: 7-10), the LL angle was found significantly changed between the groups. However, there was no relationship between the location of the major curve or the location of pain and pain intensity (Table 4).

DISCUSSION

To our knowledge, this is the first study to determine the MPS in AIS patients and evaluate the relationship between MPS and spinal coronal and sagittal alignment, location of pain, location of the major curve, and aesthetic appearance of the patients. Based on the results, AIS patients with MPS had older age, greater curvature, decreased CL, increased TK, and LL and more asymmetrical trunk appearance compared to AIS patients without pain. Additionally, decreased CL angle was found as a risk factor for MPS in AIS, and increased LL angle was associated with increased pain intensity. However, pain intensity was not related to the location of pain and the location of the major curve.

Back pain is a common complaint of AIS patients[4]. AIS patients have more back pain complaints compared to the non-scoliosis population[2,5,20]. According to Théroux et al.[2] study results, spinal pain is mostly seen in the main thoracic and lumbar regions. Similarly, it was found predominantly in the lumbar and main thoracic parts of the spine in the present study. The pain intensity of the AIS patients was documented as mild or moderate in the literature[3]. Similarly, in the current study, the pain intensity of the participants was found to be mild and moderate level.

Increased muscle tension and muscle weakness have been shown to contribute to TrP formation in MPS[21]. It was shown that the paraspinal muscle activation on the concave side was increased in the surface electromyography examinations performed in patients with AIS[22]. This spinal asymmetry supported the presence of pain in AIS[23]. Based on this information, when the

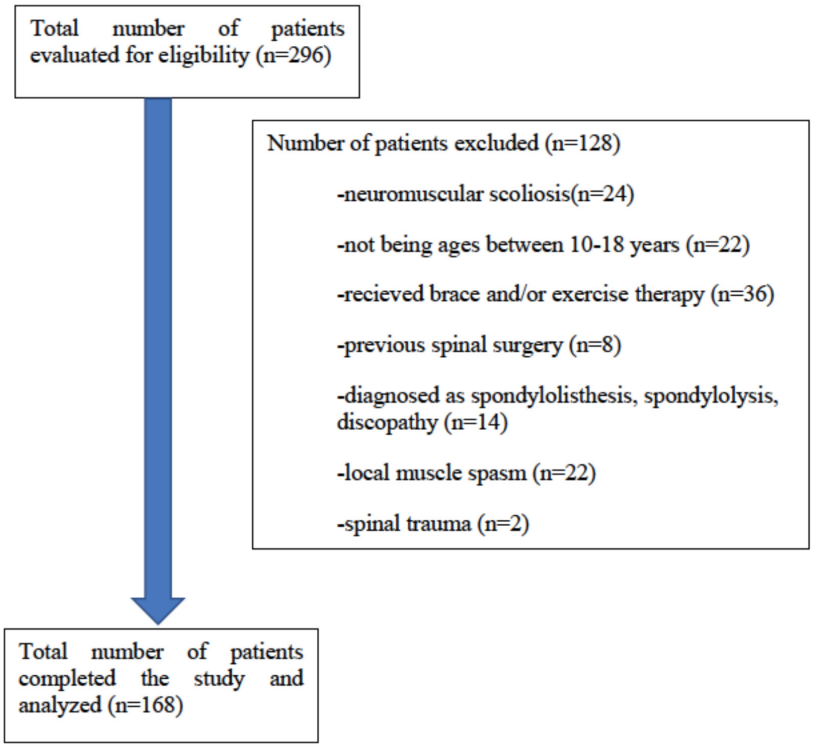

Figure 1. The flow diagram of the study

Table 1. Demographic and clinical characteristics of the participants

	MPS group (n=106)	Non-MPS group (n=62)	Total (n=168)	p
Age (years)/mean (SD)	15.3 (1.9)	14.1 (2.2)	14.9 (2.2)	0.384
Gender (n)/female/male	76/30	42/20	118/50	0.588
Risser classification/median (min-max)	4 (0-5)	3 (0.5)	4 (0-5)	0.186
Tanner stage/median (min-max)	3 (1-5)	3 (1-5)	3 (1-5)	0.152
Lenke classification (%)				0.708
Lenke 1	32 (30.2%)	23 (37.1%)	55 (32.7%)	-
Lenke 2	8 (7.5%)	1 (1.6%)	9 (5.4%)	-
Lenke 3	3 (2.8%)	3 (4.8%)	6 (3.6%)	-
Lenke 4	1 (0.9%)	1 (1.6%)	2 (1.2%)	-
Lenke 5	42 (39.6%)	32 (51.6%)	74 (44%)	-
Lenke 6	20 (18.9%)	2 (3.2%)	22 (13.1%)	-
TRACE/mean (SD)	5.3 (2.2)	4.5 (2.4)	5.02 (2.3)	0.564
VAS/mean (SD)	4.6 (1.7)	-	-	-
Pain intensity n (%)				
Mild pain	54 (51%)	-	-	-
Moderate pain	35 (33%)	-	-	-
Severe pain	17 (16%)	-	-	-
Location of the major curve n (%)				0.618
Proximal thoracic	4 (3.8%)	1 (1.6%)	5 (3%)	-
Main thoracic	41 (38.7%)	24 (38.7%)	65 (38.7%)	-
Thoracolumbar	32 (30.2%)	23 (37.1%)	55 (32.7%)	-
Lumbar	29 (27.4%)	14 (22.6%)	43 (25.6%)	-
Location of the pain n (%)				
Proximal thoracic	12 (7.1%)	-	12 (7.1%)	-
Main thoracic	39 (23.2%)	-	39 (23.2%)	-
Thoracolumbar	15 (8.9%)	-	15 (8.9%)	-
Lumbar	40 (23.8%)	-	40 (23.8%)	-

MPS: Myofascial pain syndrome, SD: Standard deviation, TRACE: Trunk Aesthetic Clinical Evaluation, VAS: Visual analog scale, min: Minimum, max: Maximum

Table 2. Inter-group analysis of the variables in the study

	MPS group (n=106)	Non-MPS group (n=62)	p	95% Confidence interval of the difference	
				Lower	Upper
Age (year)	15.3 (1.9)	14.1 (2.2)	0.001*[a]	-1.89	-0.53
Cobb angle (°)	22.2 (8.5)	19.4 (6.7)	0.018*[a]	-5.19	-0.49
CL (°)	14.9 (10.6)	19.2 (11.0)	0.016*[a]	0.79	7.60
TK (°)	42.3 (15.3)	37.6 (11.1)	0.024*[a]	-8.71	-0.62
LL (°)	53.0 (13.8)	47.3 (13.6)	0.011*[a]	-9.98	-1.32
TRACE	5.3 (2.2)	4.5 (2.4)	0.031*[a]	-1.51	-0.07
Coronal balance (mm)	6.6 (6.6)	8.5 (8.6)	0.210[b]	-0.67	4.36
PT (°)	9.1 (10.5)	10.4 (9.6)	0.516[b]	-1.87	4.42
SS (°)	31.4 (20.2)	34.6 (15.4)	0.450[b]	-2.29	8.67
PI (°)	38.1 (25.8)	43.5 (19.9)	0.340[b]	-1.66	12.40
SVA (°)	17.9 (14.6)	17.4 (16.4)	0.435[b]	-5.52	4.48

[a]Analysed with independent t-test, [b]Analysed with Mann-Whitney U test, *p<0.05 is considered for significance.
MPS: Myofascial pain syndrome, CL: Cervical lordosis, TK: Thoracic kyphosis, LL: Lumbar lordosis, TRACE: Trunk Aesthetic Clinical Evaluation, PT: Pelvic tilt, SS: Sacral slope, PI: Pelvic incidence, SVA: Sagittal vertical axis

presence of MPS was evaluated in the participants with AIS, it was seen that 63.1% of the participants were diagnosed with MPS by Travel & Simon's diagnostic criteria. According to Teles et al.[19], the prevalence of back pain in the past 30 days was 85.8%. However, Sato et al.[24] showed that 58.8% of the AIS patients had back pain. In another study, the prevalence of back pain was stated as 47.3%[3]. The prevalence of MPS in the current study was obtained by excluding other causes of spinal pain. The difference between the results can be explained by this situation.

In several studies, the location of back pain was found related to the location of the major curve[3,19]. Similarly, in the present study, there was a significant relationship between the location of the myofascial pain originating from the TrP and the location of the major curve. On the other hand, the pain intensity was not found to be related to the location of the major curve, and curve size, whereas the greater curve size was significantly related to the presence of MPS in AIS in the current study. These results were similar to previous studies[3,25,26].

Teles et al.[19] found a relationship between low back pain and lower LL angle. Conversely, in Makino et al.[27] study, increased LL was determined as a risk factor for the presence of back pain. In the present study, similar to Makino et al.'s.[27] result, there was a positive relationship between pain intensity and greater LL angles. As is known, hypokyphosis is a common finding in AIS and is associated with pain in adult spinal deformity[28]. The relationship between back pain and hypokyphosis has also been demonstrated in AIS[19]. In the current study, although the participants were hypokyphotic, those with AIS and MPS had a higher TK angle than those without pain. Several studies showed that decreased CL was associated with pain[9,29].

Additionally, McAviney et al.[29] reported a significant relationship between CL below 20 degrees and the presence of pain. In the current study, the mean CL angle was 16.5±10.9 degrees, and decreased CL was found as a risk factor for MPS in AIS. Deep flexor muscles support the CL[30]. Decreased CL may be associated with the presence of TrP in deep flexor muscles.

Aesthetic appearance is accepted as one of the main goals of treatment in AIS[16]. In the current study, it was found that participants with AIS and MPS had the worst aesthetic appearance compared to participants with AIS without pain. This was the first time to investigate the relationship between pain and aesthetic appearance. Back pain is related to biopsychosocial factors in AIS patients[30]. This result may be related to the relationship between pain perception and psychological aspects of having scoliosis. Further studies are needed to clarify this.

Table 3. Multiple regression analysis between presence of myofascial pain, participants' characteristics, scoliosis severity, and sagittal spino-pelvic parameters stratified by presence of myofascial pain

	Presence of MPS			
	β	Exp (β)	95% CI (lower-upper)	p
Age	0.162	1.176	(0.83-1.66)	0.355
Cobb angle	0.047	1.048	(0.98-1.12)	0.143
TRACE	0.072	1.074	(0.88-1.31)	0.482
CL	-0.04	0.960	(0.93-0.99)	0.026*
TK	0.025	1.026	(0.99-1.06)	0.168
LL	0.013	1.013	(0.98-1.05)	0.479
Coronal balance	-0.017	0.983	(0.93-1.04)	0.550
Risser				
Stage 0	(Reference)			
Stage 1	-0.511	0.600	(0.09-4.07)	0.601
Stage 2	-1.876	0.153	(0.02-1.33)	0.089
Stage 3	-0.266	0.766	(0.09-5.90)	0.798
Stage 4	-0.667	0.513	(0.06-4.68)	0.554
Stage 5	-0.538	0.584	(0.04-8.54)	0.694
Tanner stage				
Stage 1	(Reference)			
Stage 2	0.158	1.172	(0.17-7.99)	0.872
Stage 3	1.167	3.212	(0.46-22.35)	0.239
Stage 4	0.042	1.043	(0.12-8.68)	0.969
Stage 5	1.294	3.647	(0.25-52.18)	0.341

*p<0.05 is considered for significance
MPS: Myofascial pain syndrome, SD: Standard deviation, CL: Cervical lordosis, TK: Thoracic kyphosis, LL: Lumbar lordosis, TRACE: Trunk Aesthetic Clinical Evaluation, CI: Confidence interval

This study is important for the clinical evaluation of patients with scoliosis and back pain. The results suggested that the source of pain in these patients might be MPS. To our knowledge, this is the first study to investigate the relationship between MPS and coronal and sagittal alignment in AIS. Also, prospective study design can be accounted as a strength of the study.

Study Limitations

There are also some limitations of this study. These results may not apply to moderate to severe and severe scoliosis. Additionally, pain could be classified as chronic or acute pain. Also, it was a cross-sectional study, so the presence of instant pain was investigated. Longitudinal studies can be designed to prevent this situation.

Table 4. Comparison of the outcome measures between three subgroups in MPS-group

	Mild pain (n=54)	Moderate pain (n=35)	Severe pain (n=17)	p[a]	p[b]	95% CI of the difference	
						Lower	Upper
Cobb angle (°)	22.4 (8.3)	23.1 (9.3)	20.1 (7.5)	0.631	Mild-mod: 0.976	-5.44	0.4.02
					Mild-sev: 0.678	-3.25	7.66
					Mod-sev: 0.550	-3.10	8.94
TRACE	5.0 (2.0)	5.7 (2.2)	5.2 (2.7)	0.302	Mild-mod: 0.370	-1.82	0.45
					Mild-sev: 0.993	-2.05	1.69
					Mod-sev: 0.884	-1.44	2.45
CL (°)	14.7 (10.9)	15.4 (11.7)	14.7 (7.5)	0.935	Mild-mod: 0.987	-6.80	5.31
					Mild-sev: 1.000	-5.90	5.81
					Mod-sev: 0.992	-5.97	7.36
TK (°)	40.2 (13.9)	43.3 (16.7)	46.8 (16.1)	0.151	Mild-mod:0.370	-1.82	0.45
					Mild-sev: 0.993	-2.05	1.69
					Mod-sev: 0.884	-1.44	2.45
LL (°)	49.8 (11.6)	54.1 (16.8)	60.6 (10.4)	0.008*	Mild-mod: 0.485	-12.23	3.78
					Mild-sev: 0.003*	-18.28	-3.26
					Mod-sev: 0.250	-15.94	2.85
SVA (°)	19.7 (17.9)	15.5 (10.0)	16.9 (10.5)	0.891	Mild-mod: 0.408	-3.02	11.42
					Mild-sev: 0.809	-5.87	11.54
					Mod-sev: 0.960	-9.08	6.35
PT (°)	8.5 (10.7)	11.5 (8.9)	6.5 (12.3)	0.142	Mild-mod: 0.394	-8.13	2.09
					Mild-sev: 0.915	-6.57	10.50
					Mod-sev: 0.384	-3.59	13.56
PI (°)	36.2 (25.0)	42.8 (24.1)	34.3 (31.6)	0.964	Mild-mod: 0.520	-19.58	6.36
					Mild-sev: 0.995	-19.74	23.52
					Mod-sev: 0.709	-13.70	30.70
SS (°)	31.9 (20.0)	32.1 (18.9)	27.9 (24.1)	0.377	Mild-mod: 1.000	-10.42	10.14
					Mild-sev: 0.901	-12.52	20.59
					Mod-sev: 0.900	-12.82	21.17
Location of the curve n (%)				0.131	-	0.04	0.34
Thoracic	21 (38.9%)	20 (37%)	13 (24.1%)	-	-	-	-
Thoracolumbar	14 (40%)	7 (20%)	14 (40%)	-	-	-	-
Lumbar	10 (58.8%)	5 (29.4%)	2 (11.8%)	-	-	-	-
Location of the pain n (%)				0.568	-	0.03	0.32
Thoracic	24 (44.4%)	23 (42.6%)	7 (13%)	-	-	-	-
Thoracolumbar	20 (57.1%)	11 (31.4%)	4 (11.4%)	-	-	-	-
Lumbar	7 (41.2%)	6 (35.3%)	4 (23.5%)	-	-	-	-

p[a]: Significance value for inter-group analysis, p[b]: Significance value for post-hoc analysis, *p<0.05 is considered for significance.
MPS: Myofascial pain syndrome, CL: Cervical lordosis, TK: Thoracic kyphosis, LL: Lumbar lordosis, TRACE: Trunk Aesthetic Clinical Evaluation, PT: Pelvic tilt, SS: Sacral slope, PI: Pelvic incidence, SVA: Sagittal vertical axis, mod: Moderate, sev: Severe, CI: Confidence interval

CONCLUSION

In conclusion, MPS should be remembered as a source of pain in AIS. Although the pain severity did not change, a relationship was found between the presence of myofascial pain and spinal alignment and curve magnitude. In the future, studies investigating the pain sub-groups in AIS will be affected positively in terms of providing effective treatment methods.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, İstanbul Kanuni Sultan Süleyman Training and Research Hospital Ethical Board in conformity with the Declaration of Helsinki (under number: KAEK/2020.07.128).
Informed Consent: Written and verbal consent forms were obtained from the participants.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.D.K., M.K., Y.F.A., T.A., Concept: M.D.K., M.K., T.A., Design: M.D.K., M.K., T.A., Data Collection or Processing: M.D.K., M.K., Y.F.A., T.A., Analysis or Interpretation: M.D.K., M.K., Literature Search: M.D.K., Writing: M.D.K., M.K.
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ORIGINAL ARTICLE
8

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TREATMENT OPTIONS AND SURGICAL INDICATIONS IN SPINAL METASTASIS CASES: SINS AND NOMS CLASSIFICATIONS

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ABSTRACT

Objective: Spinal metastases are the most common tumors of the spine, constituting approximately 90% of masses encountered on spinal imaging. Spinal metastases are more commonly found as bone metastases, but are not limited to bone metastases, and approximately 20% present with symptoms of spinal canal invasion and cord compression.

Materials and Methods: A total of 32 patients who were operated for spinal bone metastases in our clinic between April 2020 and April 2022 were examined retrospectively with digital file records and imaging.

Results: Of the 32 patients included in our study, 5 (15.6%) were operated for cervical, 21 (65.6%) for thoracic, 8 (25%) for lumbar, 2 (6.25%) for sacral spinal bone metastases. There were multiple metastases in 7 (21.8%) patients. Twenty of the patients (62.5%) were male and 12 (37.5%) were female. The mean age was 67.3±13.8 years. According to the Tomita scoring, the mean was 4,8 (minimum 2-maximum 7). When the Frankel scoring of the patients was performed, 6 (18.75%) patients were B grade, 1 (3.1%) patient was C grade, and 25 (78.1%) patients were E grade. Patients with a Spinal Instability Neoplastic Score (SINS) value above 7 were considered suitable for surgery. In our study, the mean SINS was 11.1 (minimum 7, maximum 17). All patients were evaluated according to the neurologic, oncologic, mechanical, and systemic (NOMS) framework. Patients who were not suitable for surgery according to the NOMS evaluation were referred for radiotherapy/chemotherapy and weren't included in the study.

Conclusion: The decision-making process is difficult in patients with metastatic spinal disease. The surgeon must take into consider the purpose of the intended surgery (to counteract pain and preserve or restore neurological function) and the physical ability of each patient to withstand such a surgery.

Keywords: SINS, Frankel scale, spinal metastasis, tomita classification, multidisciplinary approach, NOMS

INTRODUCTION

Bone metastases are a prevalent disease, including lung, breast, prostate, kidney, and some thyroid cancers, as well as hematological malignancies especially multiple myeloma that can be considered generating tumors. About 10-15% of cancer patients have metastases to the spine[1]. Spinal bone metastases are seen in approximately 5% of cancer cases diagnosed each year. The skeletal system is the third most familiar site of metastasis, it is coming after lung and liver metastasis. Likewise, the spine is a familiar region for metastases, throughout the skeletal system. The thoracic part is the most common region within the spine. While the vertebral body is comprised of 80-85% of metastases, the posterior elements are comprised of 20-25%. The most common primary source of metastatic tumors of the spine is breast cancer. After that; lung cancer, prostate cancer, and hematological malignancies follow breast cancer. Of all tumors, multiple myeloma has the highest proclivity for spinal metastases. Various sarcoma and neuroblastoma metastases are more common in children[2].

Spine metastases can cause a vertebra to weaken or fracture. The tumor may enlarge or cause the vertebra to fracture, causing compression of the spinal cord or nerve root. Patients with spinal cord compression (SpCC) are at risk for paralysis of body structures below the compression level, weakness in limb movement, urinary/fecal incontinence, and impaired sexual function. Early targeted therapy is to prevent, reduce or delay serious adverse outcomes. Diagnostic imaging methods comprise plain radiography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography, single photon emission CT and radionuclide bone scan.

Together with cancer histology, neurological status, and overall survival, patient characteristics such as Karnofsky score, other medical comorbidities, and nutritional status should be

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conceived not only when making an operation decision, but also in selecting the proper surgical procedure. The goals of treatment of spinal bone metastatic lesions are to inhibit neurologic regression, relieve pain, reestablish neurologic status, and stabilize ranges of motion of the spine. Generally, palliation and improving quality of life are the goals. However, there is uncertainty about the effectiveness of these treatment modalities.

MATERIALS AND METHODS

A total of 32 patients who were operated on for spinal bone metastases in our clinic between April 2020 and April 2022 were examined retrospectively with digital file records and imaging. This study was approved by the Ankara City Hospital Clinical Research Ethics Committee (decision no: E1/2948/2022, date no: 05.10.2022), and written informed consent was obtained for each patient. All patients underwent MRI and/or CT scanning preoperatively and postoperatively. Advanced imaging methods were used in all patients with ambiguous metastatic lesions. Data such as pathology, surgical approach, clinical features, demographic variables, and location were analyzed retrospectively. The neurological status of the patients was evaluated using the Frankel grading system. Frankel A, B, and C were considered "Poor", and Frankel D and E's neurological status was considered "Good".

Spinal Instability Neoplastic Score (SINS) was also evaluated in patients. The SINS eventuates of 6 components. These components are the level of the metastatic spinal bone lesion, the characteristic of the metastasis (lytic or blastic), spinal alignment, the extent of vertebral body collapse, the existence of mechanical pain, and involvement of the posterolateral elements. The sum of these parameters results in an overall score between 0 and 18 divided into 3 spinal stability categories. 0-6 points constitute the stable group, 7-12 points the potential spinal instability group, and 13-18 points the unstable spinal lesion group[3]. Patients with a SINS score of ⩾7 are candidates for surgical intervention. Spinal instability is thought to be related to higher pain scores and more remarkable deterioration in physical function stated by the patient[4] (Table 1).

Neurologic, oncologic, mechanical, and systemic (NOMS) is a classification system that combines four basic evaluations: Neurological, oncological, systemic disease, and mechanical instability. The purpose of NOMS that to determine the use of systemic therapy, surgery, and/or radiation for the treatment of spinal metastases. Additionally, NOMS obtain health workers with a common language across disciplines to support select treatment plans for each patient and encourage outcome analysis between institutions[5] (Table 2).

Neurological assessment in NOMS is an assessment of the functional radiculopathy, myelopathy, and degree of epidural SpCC. Oncological assessment is based on the expected tumor response and continuity of response to current treatment modalities such as surgery, immunotherapy, conventional external beam radiation therapy, chemotherapy, stereotactic radiosurgery, or hormones. Mechanical instability is another issue described for pathological fractures; treatment options include pedicle screw, percutaneous cement application, brace application, and/or decompression surgery. The 4th evaluation is the medical comorbidities, the extent of systemic disease, assessment of the patient's ability to tolerate a recommended therapy, and expected overall patient survival relying on the extent of metastatic spinal bone lesions and tumor histology[5]. Tomita et al.[6] compiled the results of patients with spinal bone metastases who had surgical interventions and presented a classification. They designed a 10 point scale that takes into consideration the extent of bone metastases and tumor histology. The scale aims to determine the purpose of the treatment and thus the aggressiveness of the surgery. In the report, the treatment goal of patients with rapidly growing tumors and systemic metastases, such as lung or stomach, is terminal care or mostly short-term palliation; therefore these patients are suitable for supportive care or limited palliative decompression surgery, solely. Nonetheless, patients with solitary spinal metastases and slow-growing tumors such as breast or thyroid cancers are nominees for extensive or marginal excision of the spinal bone metastasis tumor for long-term control[6]. In our study, we classified the patients according to the Tomita score.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 13.0 for Windows (SPSS Inc., Chicago, IL). Continuous variables were compared with the t-test and categorical variables were compared with the chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 32 patients included in our study, 5 (15.6%) were operated on for cervical, 21 (65.6%) for thoracic, 8 (25%) for lumbar, and 2 (6.25%) for sacral spinal bone metastases. There were multiple metastases in 7 (21.8%) patients. Twenty of the patients (62.5%) were male and 12 (37.5%) were female. The mean age was 67.3±13.8 years. According to the Tomita scoring, the mean was 4.8 (minimum 2 - maximum 7). When the initial complaints of the patients were examined, 8 (25%) were found to have weakness in the extremities, 16 (50%) had vertebral pain, and 6 (18.75%) had no active complaints, but cancer was detected during screening. When the Frankel scoring of the patients was performed, 6 (18.75%) patients were B grade, 1 (3.1%) patient was C grade, and 25 (78.1%) patients were E grade. When the post-op neurological examination was evaluated, the neurological examination of the patient with Frankel grade C did not change, while the deficits of two patients with grade B increased and became grade A. There was some improvement in the deficits of the other 4 patients

Table 1. Spinal Instability Neoplastic Score

		Score
Location	Junctional (occiput-C2, C7-T2, T11-L1, L5-s1)	3
	Mobile spine (C3-6, L2-4)	2
	Semirigid (T3-T10)	1
	Rigid (S2-S5)	0
Pain	Yes	3
	Occasional pain but not mechanical	1
	Pain-free lesion	0
Bone lesion	Lytic	2
	Mixed (lytic/blastic)	1
	Blastic	0
Radiographic spinal alignment	Subluxation/translation present	4
	De novo deformity (kyphosis/scoliosis)	2
	Normal alignment	0
Vertebral body collapse	>50%	3
	<50%	2
	No collapse with >50% body involved	1
	None of the above	0
Posterolateral involvement of spinal elements	Bilateral	3
	Unilateral	1
	None of the above	0
Total score	Stable	0-6
	Indeterminate	7-12
	Unstable	13-18

Table 2. Neurologic, oncologic, mechanical, and systemic decision framework

Neurologic	Oncologic	Mechanical	Systemic	Decision
Low-grade ESCC + no myelopathy	Radiosensitive	Stable		cEBRT
	Radiosensitive	Unstable		Stabilization followed by cEBRT
	Radioresistant	Stable		SRS
	Radioresistant	Unstable		Stabilization followed by SRS
High-grade ESCC ± myelopathy	Radiosensitive	Stable		cEBRT
	Radiosensitive	Unstable		Stabilization followed by cEBRT
	Radioresistant	Stable	Able to tolerate surgery	Decompression/stabilization followed by SRS
	Radioresistant	Stable	Unable to tolerate surgery	cEBRT
	Radioresistant	Unstable	Able to tolerate surgery	Decompression/stabilization followed by SRS
	Radioresistant	Unstable	Unable to tolerate surgery	Stabilization followed by cEBRT

Stabilization options include percutaneous cement augmentation, percutaneous pedicle screw instrumentation, and open surgery.
ESCC: Epidural spinal cord compression scale (grade 0-1= low-grade, grade 2-3= high-grade), cEBRT: Conventional external beam radiation, SRS: Stereotactic radiosurgery

with grade B, which was evaluated as grade C. There was no change in patients with Frankel classification grade E. Six of the patients (18.75%) had a history of previously diagnosed cancer. Pathology was determined as lung cancer in 11 (34.3%) patients (such as squamous cell, small cell, adenocarcinoma), pathology in 7 (21.8%) patients as breast cancer, pathology in 1 (3.1%) patient as prostate cancer, pathology in 1 (3.1%) patient as multiple myeloma, and pathology as lymphoma in 12 (37.5%) patients (Table 3).

Patients with a SINS value above 7 were considered suitable for surgery. In our study, the mean SINS was 11.1 (minimum 7, maximum 17). All patients were evaluated according to the NOMS framework. Patients who were not suitable for surgery according to the NOMS evaluation were referred for

Table 3. Patient characteristics and clinical presentations

		n	%
Sex	Male	20	62.5
	Female	12	37.5
Age (years)*		67.3±13.8	69 (44-77)
Localisation	Cervical	5	15.6
	Thoracic	21	65.6
	Lumbar	8	25
	Sacral	2	6.25
	Multiple	7	21.8
Tomita score		4.8 (minimum 2, maximum 7)	
Frankel scale (preop-postop)	Grade A	0-2	0-6.25
	Grade B	6-0	18.75-0
	Grade C	1-5	3.1-15.6
	Grade D	0-0	0-0
	Grade E	25-25	78.1-78.1
Pathology	Lung	11	34.3
	Breast	7	21.8
	Prostate	1	3.1
	Multiple myeloma	1	3.1
	Lymphoma	12	37.5
Spinal Instability Neoplastic Score		11.1 (minimum 7, maximum 17)	

*Mean ± standard deviation/median (minimum - maximum)

radiotherapy/chemotherapy and were not included in the study. Data analysis was performed using IBM SPSS 26.0 (Armonk, NY: IBM Corp.) statistical analysis program. Descriptive statistical methods (frequency, percentage, mean, standard deviation, median, minimum – maximum, etc.) were used to compare data.

DISCUSSION

The most common route of spread to the spine is hematogenous spread. The main reason for this spread is the paravertebral plexus (Batson's plexus), which does not have a valve structure. Afterward, the tumor spreads to other spines with tumor embolism[7]. This usually causes patients to have multiple involvements. In addition, the reflection of venous blood return to intervertebral veins because of increased intrathoracic and intra-abdominal pressure also strengthens multiple metastases. Consequently, spinal bone metastases following this metabolic pathway cause a specific pattern of bone spread. Because of its avascular nature, the intervertebral disc is generally spared from tumor involvement: After all, the more often and seriously involved part of the vertebra is the vertebral body (approximately 80-85%), followed by lateral and posterior elements such as pedicle, lamina, etc. These reasons explain why most spinal bone metastases are located anterior to the spinal cord or dural sac, resulting in an anterior epidural compression[8,9]. Most spinal bone metastases' locations are extradural. In addition, only 5% of spinal bone metastases are intradural and less than 1% are intramedullary[9].

The clinical characteristics of spinal bone metastasis are mainly progressive deformity, neurological deficit, pain, and symptoms related to tumor origin. Pain may be localized to a specific structure and level of the spine or radicular pain. The pain may be due to bone involvement, instability caused by metastasis, or compression of neuronal tissues. The spectrum of pain is quite wide. It is stated that the pain is constant and dull, but predominant at night and is generally not affected by the arrangement of physical activities. In general, progressive, dull pain that occurs in a patient with known cancer or may become more pronounced in the elderly is suggestive of spinal metastasis[10,11].

Since most metastatic lesions begin in the vertebral body, anterior SpCC can be anticipated. Therefore, spastic paraparesis occurs clinically, which might eventually end up paresis[12,13]. Usually, this paraparesis is followed by sensory deterioration. It may proceed slowly, but it always has the potential to deteriorate within days. In the advanced stage of compression; bladder paresis, sphincter dysfunction, and sensory impairments are observed. Bladder paresis and sphincter dysfunction are generally irreversible if it persists for more than 48 hours[12-14].

For the treatment of metastatic spine tumors, SINS is an ideal classification for the detection of surgical options. NOMS is a broader treatment evaluation system. While minimizing treatment-related morbidity with this classification, it should emphasize durable tumor control by considering effective pharmacological, surgical, and radiation treatment options to approach this goal. NOMS ensures a framework that enables decision-making and can optimize patient care and treatment.

The therapeutic decision in elderly patients with spinal metastases is particularly difficult when they have remarkable comorbidities alongside metastatic disease. Nowadays, there are mainly four treatment modalities after steroid administration. These modalities are radiation, surgery, bisphosphonates, and, rarely, chemotherapy[15,16]. Another possibility is a combination of all of the above. Factors such as therapeutic control of the primary tumor, tumor stage, histological tumor type, and tumor dissemination are the main factors that determine the effectiveness of treatment modalities and the overall survival of patients. The life expectancy in this category of patients is approximately 12 months.

SpCC is not the only indication for treatment, but also by evaluating the main parameters of quality of life such as pain, mobility, and motor deficit. Perhaps the most important criterion when planning surgery for the patient is the patient's general condition is good enough to allow surgery safely. In addition, the patient's life expectancy of more than 6 months is another criterion for the indication of surgery. The latter, increasingly, the 6 month rule may be exceeded depending on the type of surgical treatment options that must be selected. Minimal invasive surgical approaches that result in faster recovery and less surgical trauma can be applied to these patients. In our study, we evaluated these criteria while making the surgical decision. Many of the criteria used for surgery cannot be treated rigidly and must be evaluated in an interdisciplinary decision-making process.

Study Limitations

In our study, there were certain limitations. First, this study was constituted in a retrospective manner. All patients were selected from patients suitable for surgery according to the NOMS framework, SINS classification, and Tomita classification. More studies with different designs and comparisons of the selective group with a non-selective group.

CONCLUSION

Patient factors such as performance/nutritional status and medical comorbidities should be considered, as well as cancer histology and life expectancy, to decide whether surgery is appropriate and to select the appropriate surgical procedure and approach. SINS and NOMS are valuable classifications for determining appropriate approaches.

Ethics

Ethics Committee Approval: This study was approved by the Ankara City Hospital Clinical Research Ethics Committee (decision no: E1/2948/2022, date no: 05.10.2022).

Informed Consent: Written informed consent was obtained from all patients for the publication of this report and accompanying images.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.G., A.D., Concept: Z.D., A.D., Design: E.Ç., A.D., Data Collection or Processing: E.Ç., Z.D., Analysis or Interpretation: G.G., E.Ç., Literature Search: G.G., E.Ç., Z.D., Writing: G.G., E.Ç.

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RELATIONSHIP BETWEEN FACET TROPISM, LUMBAR DEGENERATION AND FACET DEGENERATION

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ABSTRACT

Objective: Low back pain is a very common public health problem. Lumbar degeneration, facet degeneration and facet tropism, which are common problems that can cause lower back pain, are the most common causes of lower back pain. In this study, we examined the relationship between these pathologies.

Materials and Methods: A total of 240 patients were included in our prospectively planned study. Age, gender, height, weight, smoking history and duration, duration of pain and visual analog scale (VAS) of the patients were recorded. Intervebral disc degeneration, facet degeneration and facet tropism at three lumbar levels (L3-4, L4-5, L5-S1) were evaluated using magnetic resonance imaging and computed tomography. Intervertebral disc degeneration, according to the modified Pfirrmann Grading System; facet joint degeneration was evaluated according to the Weishaup rating. Facet joint asymmetry/tropism was defined as ≥7° difference between left and right facet joint angles.

Results: Of 240 patients, 129 (58%) were male and 111 (42%) were female. Their average height was 166.5 and their weight was 77.7. Mean pain duration was 20.4 months and VAS value was 7.67. A statistically significant ($p<0.001$) relationship was found between lumbar degeneration and facet degeneration at L3-4 and L4-5 levels. A highly significant ($p<0.001$) relationship was found between facet tropism and facet degeneration at the L4-5 level. A statistically significant relationship was found between age and lumbar degeneration and facet degeneration at all levels ($p<0.001$). A statistically significant correlation was found between age and facet tropism at L4-5 and L5-S1 levels ($p<0.001$). A statistically significant correlation was found with Facet tropism at L3-4 level, weight ($p=0.001$) and length of pain duration ($p=0.002$). A statistically significant correlation was found between facet asymmetry at L4-5 level and weight ($p=0.007$).

Conclusion: Usually, we found that lumbar degeneration and facet degeneration are related to each other and this increases with age. We determined that facet tropism had no significant effect on the other pathologies.

Keywords: Lumbar degeneration, facet degeneration, facet tropism

INTRODUCTION

Low back pain affects two-thirds of adults at least once in their lifetime[1,2]. It has become one of the biggest problems for public health in the 20th century world[3]. It is a global problem that causes loss of economic productivity and the use of health resources by applying to health institutions with complaints of pain[4].

Each lumbar segment consists of 2 facet joints posteriorly and intervertebral disc anteriorly[5]. These 3 joints carry the load together[5]. Various degenerations in these 3 joints are an important cause of low back pain[6]. There are many studies in the literature on the relationship between intervertebral disc degeneration and facet joint degeneration. However, there is no consensus on which one starts first and which triggers the other. Some of the studies have adopted that there is primarily intervertebral disc degeneration and that this leads to facet joint degeneration[7-10]. There are also studies advocating the view that facet joint degeneration causes intervertebral disc degeneration[11-15]. Apart from facet joint degeneration, another pathology of facet joints is facet joint tropism. Facet joint tropism is considered as the asymmetry of the angles of the 2 facet joints in the same segment in the lumbar and lumbosacral regions[16]. The effect of facet tropism on lumbar degeneration and the relationship between them has not yet been clearly understood[17,18]. There are various studies on whether facet joint tropism causes intervertebral disc degeneration, facet joint degeneration and thus lumbar degeneration[19,20]. As it can be understood, a clear concensus regarding lumbar degeneration and its etiology has not been obtained yet.

In our study, we aimed to examine lumbar degeneration, facet joint degeneration, facet tropism and their relationship with each other and contribute to the literature.

MATERIALS AND METHODS

A total of 240 patients who applied to our hospital's outpatient clinics with the complaint of low back pain were included in the study prospectively. Patients with previous spinal surgery history, spinal tumor, infection and fracture, lumbar spondylolisthesis

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and scoliosis were not included in the study. Age, gender, height, weight, smoking history and duration, pain duration and visual analog scale (VAS) of these patients were recorded.

Magnetic resonance imaging (MRI) and computed tomography (CT) were used to assess intervertebral disc degeneration, facet degeneration, and facet orientation/tropism. Radiological examinations were performed independently by two different senior clinicians (ÖÖ,OB.), and the average was taken. Intervebral disc degeneration, facet degeneration and facet tropism were evaluated at three lumbar levels (L3-4, L4-5, L5-S1).

Intervertebral disc degeneration is divided into 8 different grades according to the modified Pfirrmann Grading System on T2-weighted midsagittal MRI [SAG T2 FSE; repetition time (TR)=3200 ms; time of echo (TE)=100 ms; field of view (FOV)=16 cm; thickness=5 mm] (Table 1). Facet joint degeneration was divided into 4 grades according to CT scan (FOV=16 cm; thickness= 5 mm; matrix=512 512) using Weishaup grading (Table 2). Facet tropism, with the previously described technique[20,21]; the angle of the facet joint is between the anterior and posterior ends of the T2-weighted axial MRI (SAG T2 FSE; TR=3200 ms; TE=100 ms; FOV=16 cm; thickness=5 mm) articular surface and the median sagittal line of the same vertebral body. Facet joint asymmetry is defined as the difference between left and right facet joint angles ⩾7°. The measurement of facet tropism radiologically with CT sections is explained in Figure 1.

Institutional ethics approval was obtained from the Hitit University Faculty of Medicine Clinical Research Ethics Committee (decision no: 200, date no: 05.05.2020). Oral and written informed consent was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

SPSS 25.0 package program (IBM Corporation, Armonk, NY) was used for statistical analysis of the findings obtained in the study. Descriptive statistical methods (frequency, percentage, mean, standard deviation) were used to evaluate the study data, and the Mann-Whitney U test was used to evaluate the normal distribution. The Mann-Whitney U test was used to compare the quantitative data between the two groups. The Kruskal-Wallis test was used to determine the significance of the difference between the mean of the three groups in non-normally distributed groups. P<0.05 was considered significant.

RESULTS

The mean age of the 240 patients we included in the study was 41.7 (minimum: 18, maximum: 80). One hundred and twenty nine (58%) were male and 111 (42%) were female. Their average height was 166.5 and their weight was 77.7. Mean pain duration was 20.4 months and VAS values were 7.67.

A statistically significant (p<0.001) relationship was found between lumbar degeneration and facet degeneration at L3-4 and L4-5 levels. No statistically significant correlation was found at L5-S1 level (p=0.118) (Table 3).

When L3-4 (p=0.317), L4-5 (p=0.223) and L5-S1 (p=0.615) levels were analyzed, no statistically significant relationship was found between facet tropism and lumbar degeneration (Table 4). There was a highly significant (p<0.001) relationship between facet tropism and facet degeneration at the L4-5 level, but no significant correlation was found at the L3-4 (p=0.268) and L5-S1 (p=0.321) levels (Table 4).

According to age; there was a statistically significant correlation between age and lumbar degeneration (p<0.001) and facet degeneration (p<0.001) at L3-4 level. A statistically significant correlation was found between age and lumbar degeneration (p<0.001), facet degeneration (p<0.001) and facet tropism (p<0.001) at L4-5 level. A statistically significant correlation was found between age and lumbar degeneration (p<0.001), facet degeneration (p<0.001) and facet tropism (p=0.001) at L5-S1 level (Table 5).

There was no significant relationship between facet tropism and gender at three levels of L3-4 (p=0.820), L4-5 (p=0.585) and L5-S1 (p=0.215).

When L3-4, L4-5 and L5-S1 levels were examined with facet tropism, it was found that facet asymmetry at L3-4 level was

Table 1. Modified Pfirrmann grading system of lumbar disc degeneration

Grade	Signal from nucleus and inner bers of annulus	Distinction between inner and outer bers of annulus at posterior aspect of disc	Height of disc
1	Uniformly hyperintense (equal to CSF)	Distinct	Normal
2	Hyperintense (>presacral fat and <CSF)	Distinct	Normal
3	Hyperintense (<presacral fat)	Distinct	Normal
4	Mildly hyperintense (slightly > outer bers of annulus)	Indistinct	Normal
5	Hypointense (=outer bers of annulus)	Indistinct	Normal
6	Hypointense	Indistinct	<30% reduction of disc height
7	Hypointense	Indistinct	30% to 60% reduction of disc height
8	Hypointense	Indistinct	>60% reduction of disc height

CSF: Cerebrospinal fluid

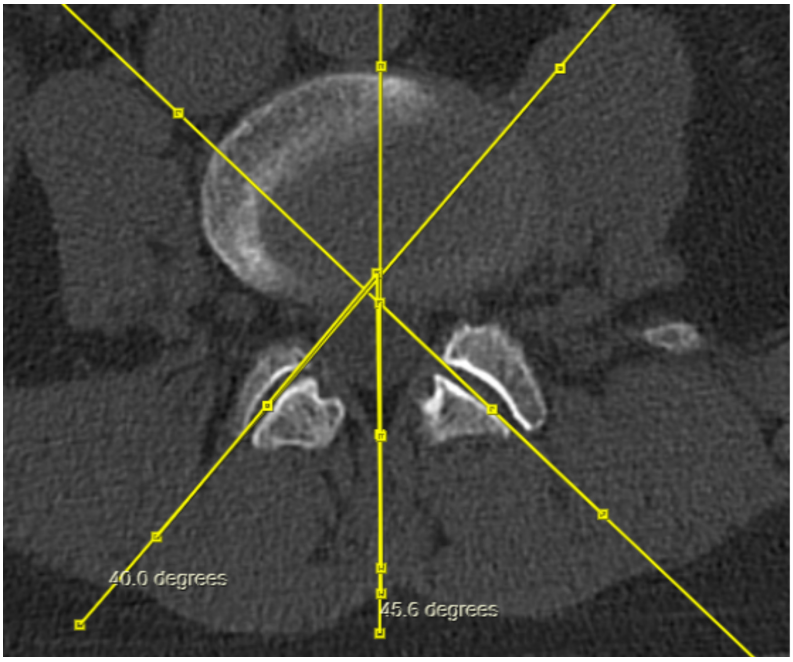

Figure 1. Two angles, one right and one left, were measured between a reference line drawn from the midline of the vertebral body in the coronal plane and the intersecting lines connecting the anteromedial and posterolateral ends of each zygapophyseal joint on the right and left sides.

Table 2. Weishaupt facet joint degeneration

Grade	Criteria
0	Normal facet joint space (2±4 mm width)
1	Narrowing of the facet joint space (`2 mm) and/or small osteophytes and/or mild hypertrophy of the articular process
2	Narrowing of the facet joint space and/or moderate osteophytes and/or moderate hypertrophy of the articular process and/or mild subarticular bone erosions
3	Narrowing of the facet joint space and/or large osteophytes and/or severe hypertrophy of the articular process and/or severe subarticular bone erosions and/or subchondral cysts

Table 3. Relationship between lumbar degeneration and facet degeneration according to levels

L 3-4	Facet degeneration p-value (r)*
Lumbar degeneration	<0.001 (0.403)
L 4-5	Facet degeneration p-value (r)*
Lumbar degeneration	<0.001 (0.355)
L5-S1	Facet degeneration p-value (r)*
Lumbar degeneration	0.118 (0.101)

*Spearman correlation test

statistically significantly correlated with weight (p=0.001) and length of pain duration (p=0.002). A statistically significant correlation was found between facet tropism at L4-5 level and weight (p=0.007) (Table 6).

DISCUSSION

Many studies have been found in the literature about pathologies such as lumbar degeneration, facet degeneration and facet tropism and their relations with each other[7-15,17-19]. In these studies, different results were obtained about the etiology of existing pathologies and the relationship between each other. While some studies have concluded that facet joint degeneration causes lumbar degeneration; in some studies, it has been concluded that lumbar degeneration causes facet degeneration[7-15]. However, the effects of the presence of facet tropism on degeneration were examined, but a clear consensus could not be reached[19-21]. Previous studies have generally been done on smaller patient populations. We studied a larger population, including 240 patients. We also examined the degeneration status according to age.

When we examine it according to the levels; a significant correlation was found between lumbar degeneration and facet degeneration at L3-4 level. However, there was no correlation between the presence of facet tropism at this level and facet degeneration and facet tropism. Again, at the L3-4 level, age and facet degeneration and lumbar degeneration were found to be statistically significantly correlated, while facet tropism was not correlated. However, a significant correlation was found between L3-4 facet tropism at the same level and pain duration and weight. We found that the duration of pain was longer

Table 4. Relationship between facet tropism and lumbar degeneration and facet degeneration by levels

L3-4	Lumbar degeneration p-value (r)*	Facet degeneration p-value (r)*
Facet tropism	0.315 (0.065)	0.268 (-0.072)
L4-5	Lumbar degeneration p-value (r)*	Facet degeneration p-value (r)*
Facet tropism	0.223 (-0.079)	<0.001 (-0.294)
L5-S1	Lumbar degeneration p-value (r)*	Facet degeneration p-value (r)*
Facet tropism	0.617 (0.032)	0.321 (-0.064)

*Spearman correlation test

Table 5. Relationship between age and lumbar degeneration, facet degeneration and facet tropism

Rel. with age	Lumbar degeneration	Facet degeneration	Facet tropism
L3-4	p<0.001*	p<0.001*	p=0.272*
L4-5	p<0.001*	p<0.001*	p<0.001*
L5-S1	p<0.001*	p<0.001*	p=0.001*

*Kruskal-Wallis test

Table 6. Relationship parameters with facet tropism

Facet tropism	Weight	Length of pain duration
L3-4	p=0.001*	p=0.002*
L4-5	p=0.007*	p=0.151
L5-S1	p=0.214	p=0.776

*Mann-Whitney U test

in those with this level of tropism. In addition, the presence of tropism appears to cause long pain duration and an increase in weight gain. The reason for this may be that patients remain immobile due to pain and gain weight.

At L4-5 level; a significant relationship was found between lumbar degeneration and facet degeneration. We found a statistically highly significant relationship between facet tropism and facet degeneration at the L4-5 level, unlike the L3-4 and L5-S1 levels. We observed that all pathologies increased with age at L4-5 level. A statistically significant relationship was found between tropism and weight at the L4-5 level, as at the L3-4 level. It is also seen at this level that facet tropism causes weight gain.

In general, a relationship was found between facet degeneration and lumbar degeneration, and it was observed that their incidence increased. In addition, no relationship was found between facet tropism and lumbar degeneration at all three lumbar levels evaluated. A significant relationship between tropism and facet degeneration was found only at L4-5 level.

There was a significant correlation between age and 3 pathologies at 3 levels, except for tropism at L3-4 level. The increase in the degeneration process with age was an expected issue in line with the literature.

Study Limitations

Our study has several limitations. First of all, although the number of patients was larger compared to other studies, it could have been done with an even larger patient population. Apart from this, L1-2 and L2-3 vertebral segments and even lower thoracic vertebrae levels could also be included in the study since they cause low back pain.

CONCLUSION

In general, we found that lumbar degeneration and facet degeneration were associated with each other and this increased with age. We determined that facet tropism was not very effective on other pathologies. We think that the difference between the existing studies in the literature and even the different results obtained in different lumbar levels of the same patient is due to the small number of patients. We think that it would be more accurate to conduct these studies on a much larger patient population.

Ethics

Ethics Committee Approval: Institutional ethics approval was obtained from the Hitit University Faculty of Medicine Clinical Research Ethics Committee (decision no: 200, date no: 05.05.2020).

Informed Consent: Oral and written informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Ö., Concept: Ö.Ö., Design: Ö.Ö., O.B., Data Collection or Processing: Ö.Ö., Analysis or Interpretation: Ö.Ö., Literature Search: Ö.Ö., Writing: Ö.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

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ULTRASONOGRAPHY IN CAUDAL INJECTIONS CAN REDUCE THE USE OF FLUOROSCOPY

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ABSTRACT

Objective: We evaluated the differences between classical, fluoroscopy-guided caudal epidural steroid injection (CESI) and ultrasonography-guided CESI in terms of pain levels and the number of fluoroscopy shots administered in patients with lower lumbar disk herniation (L4-L5, L5-S1).

Materials and Methods: All procedures were performed in an operating room under sterile conditions. In total, 28 patients who underwent CESI using ultrasonography and 28 who underwent CESI using classical fluoroscopy were randomized and retrospectively compared in terms of the number of fluoroscopy shots administered. In the ultrasonographic group, the localization of the needle was confirmed by lateral fluoroscopic imaging after the procedure. In the classical fluoroscopy group, posteroanterior and lateral fluoroscopic images were used to guide the entry of the needle into the caudal canal from the skin entry point, advance the catheter in the canal, and administer the contrast material. The patients' pain levels before and after the procedure were self-evaluated using a visual analog scale.

Results: In the classical fluoroscopy group, the mean number of fluoroscopy shots was 7.07. In the ultrasonography group, it was 1.21. In the fluoroscopy group, the mean pain scores were 8.64±0.78 before, 3.10±1.13 immediately after, and 4.64±1.96 3 weeks after the procedure. In the ultrasonography group, the mean pain scores were 8.53±0.174 before, 3.10±0.238 immediately after, and 4.60±0.376 3 weeks after the procedure.

Conclusion: The use of ultrasonography in caudal injections reduces fluoroscopy exposure and, therefore, radiation exposure.

Keywords: Ultrasonography, caudal epidural steroid injection, fluoroscopy, radiation

INTRODUCTION

The most common causes of low back and leg pain are lumbar disk herniation, lumbar spondylosis, degenerative spondylolisthesis, and previous lumbar operation[1]. In patients with low back and radicular pain due to a spinal pathology, epidural injection is known to reduce pain and improve functional status[2]. Caudal epidural steroid injection (CESI) can be considered a nonsurgical treatment method in patients with lower lumbar disk herniation (L4-L5, L5-S1) or lumbar spondylosis, in which pain cannot be relieved through medical treatment, rest, and physical therapy[3]. The caudal approach for epidural injection is easy to perform and relatively safe compared with the interlaminar and transforaminal approaches; thus, the risk of accidental dural puncture is reduced[4]. The caudal epidural intervention was first introduced as a block- and landmark-based blind technique. The blind procedure had a success rate of >96% in children; however, in adults, this rate was only 68-75%, even with experienced practitioners[5,6]. In epidural steroid injection (ESI), long-acting local anesthetic and corticosteroids with antiedema and anti-inflammatory effects are injected into the epidural space[7]. The effectiveness of the injection depends on precise drug delivery to the putative site of pathology. The procedure is usually performed under fluoroscopy guidance, which has remarkably improved the success rate of CESI and is now considered the gold standard[8]. Fluoroscopic guidance helps confirm that the needle is correctly positioned and the drugs are properly injected into the epidural space. However, owing to the fluoroscopy-associated radiation hazard to patients and clinicians; it may not be applicable in daily practice. Intravascular injection during CESI has been reported in 3-14% of cases when conventional fluoroscopy is used, even after negative aspiration[9].

The use of ultrasound guidance for conventional caudal epidural injections is increasing[1,10,11]. Ultrasound guidance enables the localization of the sacral hiatus and visualization of the sacrococcygeal ligament; it facilitates the detection of variations, thereby making injection easy and safe[12,13]. Ultrasound guidance can be used in almost any clinical setting; it is easy to learn and radiation-free. Very high success rates of 96.9-100% have been reported in ultrasound-guided CESI[10,14]. Ultrasound is not only effective for guiding needle placement

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but also can be used to predict CESI success and reduce the time spent on fluoroscopy-guided injections. We aimed to study the effect of ultrasonography on the number of fluoroscopy shots administered (radiation exposure) in fluoroscopy-guided CESI for lower lumbar disk herniation pathologies that do not require surgical intervention.

MATERIALS AND METHODS

We retrospectively and randomly screened patients with lower back and leg pain who had been diagnosed with lower lumbar disk herniation (L4-L5 and L5-S1), unilateral or bilateral radiculopathy for >3 months, and underwent the CESI procedure between June 2019 and June 2020. We excluded patients with rapidly progressive neurological deficit, cauda equina syndrome, motor weakness, previous spinal surgery, steroid use, and a history of allergy to steroids and iodinated contrast agents. Furthermore, we excluded patients with a skin infection at the site of intervention or multiple comorbidities (e.g., hypertension, diabetes mellitus, and ischemic heart disease).

The study was approved by the Ankara City Hospital Ethics Committee (decision no: E1/913/2020, date no: 16.07.2020) of the relevant institute. Informed written consent was obtained from all patients evaluated at an outpatient clinic. The patients' age and body mass index (BMI) data were recorded. A total of 28 patients underwent the ultrasound-guided CESI procedure, and 28 patients underwent classical fluoroscopy-guided CESI. The number of fluoroscopy shots administered during the procedure was noted and intergroup comparisons were performed. All procedures were performed in an operating room in sterile conditions. The CESI procedure was performed by placing a pillow under the abdomen of the patient lying in a prone position. The operation site was subsequently cleaned with an antiseptic solution containing povidone-iodine and covered in a sterile manner. Vascular access was opened using a 20-gauge Angiocath™ (Becton Dickinson, Franklin Lakes, NJ, USA), and isotonic solution [0.9% NaCl=saline fluid (SF)] was injected. Arterial blood pressure, pulse, peripheral oxygen saturation, and electrocardiogram were monitored.

An 18-gauge Tuohy spinal epidural needle was used in the classical fluoroscopy-guided CESI procedure. Fluoroscopy was performed (OEC Fluorostar C-8; GE Healthcare, Solingen, Germany) in stages of the localization of the spinal needle on the skin for confirming its entry into the caudal hiatus, advancing the catheter in the caudal hiatus, and confirming the location with 1-2 mL of contrast material (Omnipaque; Medikim, Istanbul, Turkey). Posteroanterior and lateral images were obtained (Figure 1), and the number of fluoroscopy shots was noted. Subsequently, the sacral hiatus was determined, and local anesthesia (lidocaine, 2 mL) was applied using a 27-gauge dental-tipped (Germany) needle. Through separate injectors, the following were administered via the catheter as a 10 mL mixture: 1 mL (40 mg) methylprednisolone acetate as steroid; 40 mg/mL Depo-Medrol® (Pfizer, New York, NY, USA) with 5 mL (25 mg) bupivacaine as a local anesthetic; and Marcaine (0.5 flacons; Eczacıbaşı, Turkey), diluted with 5 mL of 0.9% NaCl=SF. The needle was inserted up to the S3 level for proper dissemination of the drug. A Christmas tree-like appearance was observed in all patients, resembling a contrast dye distribution.

For ultrasound-guided CESI, we used the Aplio 500 ultrasound machine (Toshiba, Tokyo, Japan). After sterile wrapping of the convex probe, an axial image was first obtained in the midline; the two hypoechoic sacral corns, sacrococcygeal ligament, and sacrum surface were visualized. The sacral hiatus was visualized between the sacrococcygeal ligament and sacral surface (Figure 2). The sacral canal is a triangular opening at the caudal end of the sacrum, bound laterally by two sacral corns. While the probe was on the sacral hiatus, it was rotated 90° longitudinally and the sacral base, sacrococcygeal ligament, and sacral hiatus were observed (Figure 3). The skin was then penetrated by an 18-gauge spinal needle under ultrasound guidance. As soon as the sacral hiatus was believed to have been entered, a lateral fluoroscopic image was obtained; thus, it was confirmed that the needle was in the sacral hiatus (Figure 4). When the needle was at the point of passing the sacrococcygeal ligament, without further advancement, a mixture of steroid, local anesthesia, and saline was administered at the same dose as in the other method. In both methods, negative pressure was applied to the needle and the absence of vascular leakage was confirmed. Although contrast material was administered in the fluoroscopy-guided procedure, it was not administered in the ultrasound-guided procedure. After the procedure, each patient was transferred to a postoperative follow-up room and their hemodynamic parameters were monitored for 30 min; they were subsequently moved to the ward. The patients were followed up for 2 h before being discharged and were informed about any possible complications. The patients evaluated their pain levels before, during, immediately after, and 3 weeks after the injection using a visual analog scale (VAS), with the absence of pain scoring 0 and severe pain scoring 10 on the VAS.

Statistical Analysis

Statistical Package for the Social Sciences, version 23.0 (IBM Corporation, Armonk, NY, USA), was used for statistical analyses. We tested for normality using the Shapiro-Wilk test. Descriptive statistics are reported as means with standard deviations, medians with ranges, or frequencies with percentages. We calculated 95% confidence intervals. Intergroup comparisons were performed using Student's t-test or Mann-Whitney U test. Outcomes at baseline and follow-up were analyzed using a two-way repeated-measures analysis of variance. Statistical significance was set at $p<0.05$.

RESULTS

This study included 56 patients-28 received classical fluoroscopic CESI, and the remaining 28 received ultrasound guidance-assisted CESI. In the classical fluoroscopic group,

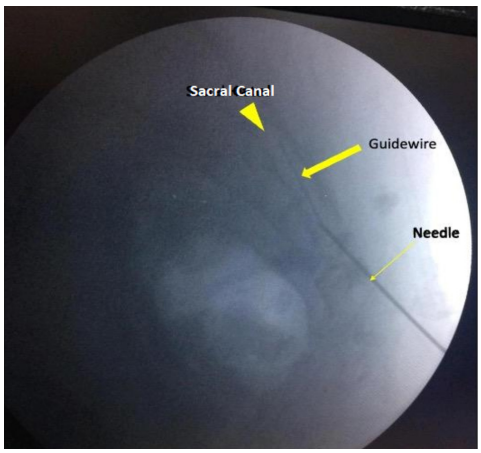

Figure 1. Lateral fluoroscopic view of catheter advancement in fluoroscopic CESI
CESI: Caudal epidural steroid injection

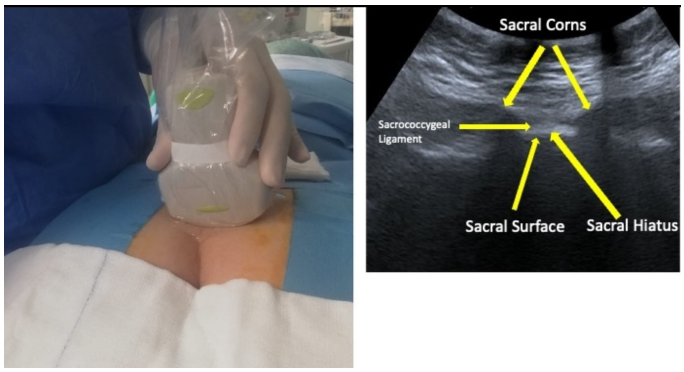

Figure 2. In the axial view of the convex ultrasound probe, two hypoechoic sacral corns, the sacrococcygeal ligament, and the sacrum surface were visualized. The sacral hiatus was visualized between the sacrococcygeal ligament and sacral surface

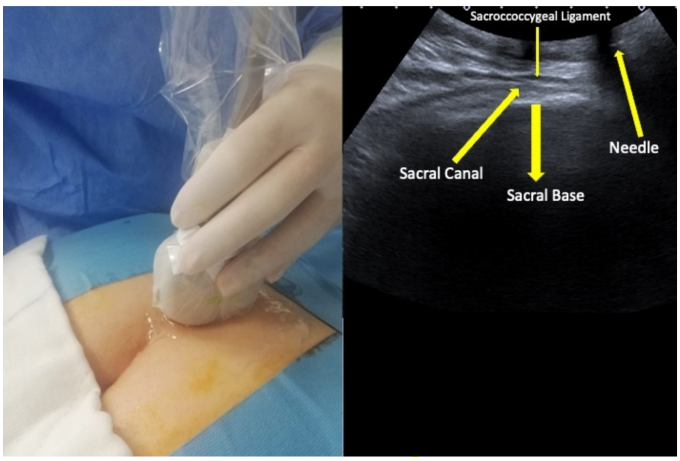

Figure 3. While the probe was on the sacral hiatus, it was rotated 90° longitudinally and the sacral base, sacrococcygeal ligament, and sacral hiatus were observed

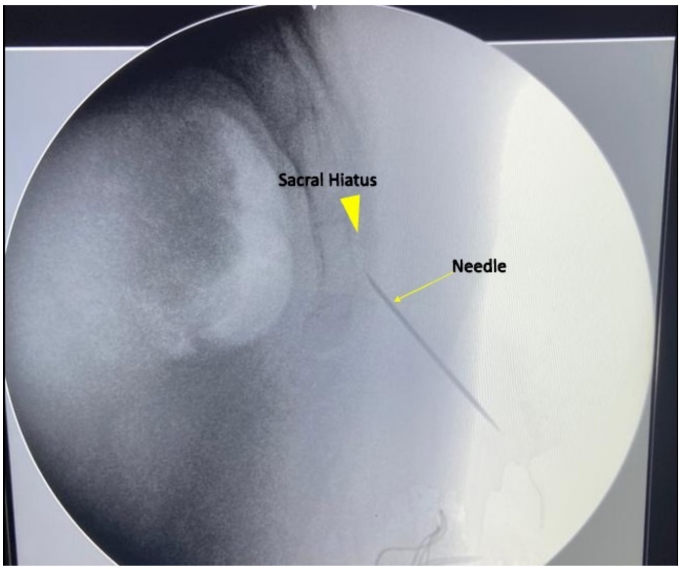

Figure 4. Lateral fluoroscopic image. It was confirmed that the needle was in the sacral hiatus

there were 10 men and 18 women (age, 48.53±10.18 years; BMI, 24.96±1.02 kg/m^2; mean symptom duration, 18.3±12.85 months). Lumbar disk pathology was at L5-S1 in 11 patients, L4-L5 in 5, and both L5-S1 and L4-L5 in 9. Nine patients had a lumbar narrow canal attached to the disk. The mean number of fluoroscopy shots administered was 7.07±0.76 (Table 1). The mean VAS pain scores were 8.64±0.78 before, 3.10±1.13 immediately after (p<0.001), and 4.64±1.96 (p<0.001) 3 weeks after the procedure (Table 1).

In the ultrasound guidance-assisted group, there were 12 men and 16 women (age, 49.35±10.75 years, BMI, 24.36±1.66 kg/m^2; mean symptom duration, 22.5±17.64 months). Lumbar disk pathology was at L5-S1 in 10 patients, L4-L5 in four patients, and at both L5-S1 and L4-L5 in five patients. Lumbar narrow canal attached to the disk was present in five patients. The mean number of fluoroscopy shots administered was 1.21±0.41 (p<0.001) (Table 1). Mean VAS pain scores were 8.53±0.174 before, 3.10±0.238 immediately after (p<0.001), and 4.60±0.376 (p<0.001) 3 weeks after the procedure (Table 1).

No significant difference was observed between the two groups in terms of mean age and sex (Table 1). The VAS pain scores after the procedure were significantly lower in both groups than before it (p<0.001) (Table 2). Furthermore, no significant difference was noted in the improvement of VAS pain scores after the procedure between the two groups (Table 3). The mean number of fluoroscopy shots was significantly lower in the ultrasound-assisted group than in the classical fluoroscopic group (p<0.001).

In one patient who received ultrasound-assisted CESI, the caudal hiatus entrance was located and medication was administered using fluoroscopy because axial imaging with the ultrasound probe could not be technically performed owing to the patient's gluteal pathology. Therefore, this patient, who received a high number of fluoroscopy shots, was not included in the evaluation. Similarly, two patients who underwent ultrasound-assisted CESI could not be confirmed using fluoroscopy because of an unexpected malfunction of the fluoroscopy device. The procedure was considered successful; the patients' pain scores decreased considerably after drug administration. However, these two patients were not included in the evaluation.

No complications were observed in either group.

DISCUSSION

The mean number of fluoroscopy shots administered to patients was significantly lower in the ultrasound-assisted group than in the classical fluoroscopic group. Thus, the ultrasound group received less radiation exposure than the fluoroscopy group. In both groups, there was an improvement in VAS pain scores immediately and 3 weeks after the procedure compared with the pre-procedure score. No significant intergroup difference was noted in terms of the improvements.

In caudal epidural injection, the sacral hiatus is a crucial bone structure with a diameter of <3.7 mm apically. This structure has been associated with difficulty in inserting a needle into the caudal epidural space using the blind technique[15]. Challenges are encountered when ultrasound is used to guide needle insertion in patients with a sacral hiatus anteroposterior diameter of <1.6 mm[11]. In our study, there was no failure during needle insertion in either group.

Several studies have reported that ultrasonography is an effective tool for the CESI procedure because it is easy to use in the evaluation of musculoskeletal diseases, provides real-time images, and does not cause radiation exposure[10,12,16]. Hazra et al.[17] reported that needle insertion time was significantly shorter using ultrasound guidance than using fluoroscopy guidance.

Needle placement in the (fluoroscopic) control subjects was performed with complete accuracy in the ultrasound-assisted procedures of our study. We did not use contrast materials in the fluoroscopic controls; we used the fluoroscopic controls only to confirm the location of the needle before drug administration. The contrast agent used in fluoroscopy to examine the distribution of the administered drug can cause various side effects such as nausea, vomiting, extensive urticaria, bronchospastic reaction, hypotension, tachycardia, and anaphylactic reactions[18,19]. Other serious complications include lower extremity myoclonic spasms and tonic seizure, leading to status epilepticus; rhabdomyolysis and disseminated intravascular coagulation have also been reported[20]. In addition to the side effects of the contrast medium, cost should also be considered. We did not use contrast material in the ultrasound guidance group; no complications were observed during the procedure or follow-ups. There is a minimal risk of intravascular injection or dural puncture when the injection is performed immediately after penetration into the sacrococcygeal ligament. Doo et al.[21] examined the effect of needle depth in caudal injection under ultrasound guidance by comparing two groups as follows: One with caudal injection performed using a traditional method after the needle was advanced 1 cm into the sacral canal, the other in which injection was performed using a new method immediately after penetration into the sacrococcygeal ligament. Subsequently, fluoroscopy with contrast material was obtained to evaluate the epidural spread of the injected materials and monitor possible complications. The incidence of intravascular injection was 24% in the first group and 0% in the second. The authors concluded that the new caudal epidural injection technique was a safe alternative to the traditional technique, with a higher success rate and lower risk of accidental intravascular injection. Their study also reported that the use of contrast to verify the accuracy of needle position in the CESI procedure was not necessary and did not confer additional benefits when performed by experienced clinicians. In our study, the injection was performed under ultrasound guidance when the needle was at the point of penetrating the sacrococcygeal ligament at an angle of approximately 45° in the position preceding advancement into the sacral canal. No

Table 1. Comparison of patients' demographics, number of fluoroscopy shots administered, and VAS before and after the procedure. Changes in the VAS score before, immediately after, and 3 weeks after the procedure

	Ultrasound (n=28)	Fluoroscopy (n=28)	p-value
Age (± SD)	49.35±10.75	48.53±10.18	0.863
Gender			
Female (n; %)	16; 57.1	18; 64.3	0.392
BMI (± SD)	24.36±1.66	24.96±1.02	0.254
Duration (month)	22.5±17.64	18.3±12.85	0.478
Level			
L4-L5 (n; %)	4; 14.3	5; 17.9	0.984
L5-S1 (n; %)	10; 35.7	11; 39.3	
Midline (n; %)	4; 14.3	4; 14.3	
Disc + narrow channel (n; %)	5; 17.9	9; 16.1	
L45 + L4-L5 + L5-S1 (n; %)	5; 17.9	9; 16.1	
Number of shots	1.21±0.41	7.07±0.76	<0.001*
VAS before	8.53±0.174	8.64±0.78	0.734
After VAS after	3.10±0.238	3.10±1.13	0.823
VAS 3rd week	4.60±0.376	4.64±1.96	0.927

*p<0.05
SD: Standard deviation, BMI: Body mass index, VAS: Visual analog scale pain score

Table 2. Changes in the VAS score before, immediately after, and 3 weeks after the procedure

	Ultrasound	p-value	Fluoroscopy	p-value
VAS before	8.53±0.174	-	8.64±0.78	-
After VAS	3.10±0.238	<0.001	3.10±1.13	<0.001
VAS 3rd week	4.60±0.376	<0.001	4.64±1.96	<0.001

SD: Standard deviation; BMI: Body mass index, VAS: Visual analog scale pain score

Table 3. Comparison of improved VAS scores between the two groups

	Ultrasound mean difference	Fluoroscopy mean difference	p-value
VAS before-after	5.41±0.29	5.53±0.28	0.810
VAS before-3rd week	3.92±0.39	4.00±0.39	0.961

VAS: Visual analog scale pain score

contrast material was used in the fluoroscopic control and no complications were observed.

In a study by Chen et al.[10], the sacral hiatus was accurately positioned by ultrasound in 70 patients; then, the caudal epidural needle was successfully inserted into the sacral hiatus and caudal epidural space, which was subsequently confirmed via contrast agent fluoroscopy. An accuracy of 100% in needle placement was reported. In our study, we also report 100% accuracy in needle placement performed with ultrasound guidance. Ultrasonography can be as effective as fluoroscopy in preventing complications during caudal epidural injection, except for intravascular and intrathecal injections[22]. Naidoo et al.[23] investigated the value of using contrast as an additional aid to verify the accuracy of needle placement for intraoperative image intensifier-guided caudal epidural injections. Correct needle placement on the first attempt was confirmed in 100% of cases. These results show that an experienced surgeon can accurately place the needle in caudal epidural injections using image intensification, without contrast.

Although fluoroscopy is the gold standard for confirming needle placement during the CESI procedure, radiation exposure is a major concern when fluoroscopic images are obtained[24,25].

The presence of an association between radiation and cancer is well known; however, the long-term effects of exposure to low radiation doses-and the known safe dose-are not completely known[26,27]. Ionizing radiation has two effects at the cellular level. First, in deterministic effects, a threshold for the occurrence of damage exists and the amount of damage increases as the dose increases. In these terms, skin injuries have been a major concern in a fluoroscopy-guided intervention[10]. Second, in cytochastic effects, the radiation effect is "all or nothing"; there is no threshold, and the effects are likely to occur even at the lowest dose levels. During medical imaging, the cytochastic effect is more probable. Chronic effects are

more likely to be the result of long-term, low-dose exposure. It is well known that cumulative exposure to radiation increases the risk of adverse health effects such as genetic effects, cataracts, circulatory diseases, and cancer[26,27].

The radiation dose is a measure of the energy stored in tissue as a result of the interaction between radiation and living tissue, measured in units of radiation absorbed dose (RAD), roentgen equivalent man (REM), grays (Gy), and sieverts (Sv). The gray unit (the international unit for RAD) represents the amount of radiation that causes 1 J energy absorption in 1 kg irradiated material (1 RAD=1 REM=1000 mRAD=1000 mREM=0.01 Gy). The international unit of measurement for the biological effects of X-rays on the human body is the Sv: 1 Sv=100 RAD (i.e., 1 Sv=1 Gy=100 RAD=100 REM or 1 REM=1 RAD=0.001 Sv).

The maximum dose for radiation workers is 20 mSv/year for five consecutive years and 50 mSv/year for a single year. For the public, the maximum dose is 10 mSv/year for five consecutive years and 5 mSv/year for a single year[28]. To avoid radiation-induced skin damage, the recommended threshold for exposure is 2 Gy and the annual exposure limit is 50 mSv[29].

As mentioned earlier, radiation is known to be associated with cancer; however, the long-term effects of exposure to low radiation doses as well as the known safe dose remain unknown. In Turkey and worldwide, the "as low as reasonably achievable" (ALARA) principle is used to reduce radiation exposure[30]. At present, to the best of our knowledge, there is no universally accepted guideline for minimizing radiation exposure in the operating room; the cumulative radiation exposure of operators is not known. The operators must follow simple radiation safety rules to minimize their exposure, such as increasing their distance from the radiation source; reducing overall exposure time; and protecting sensitive areas with lead aprons, thyroid shields, lead goggles, and lead gloves. A study by Vural et al.[31] reported that 90% of operating room workers had been exposed to fluoroscopy in the past year; 44% were exposed to fluoroscopy more than once per week. Even very low radiation doses (e.g., 0.001 RAD) are carcinogenic and exert negative effects on the skin, eyes, gonads, and blood cells. Wearing a lead apron is an important protection against radiation; a lead thickness of 0.5 reduces radiation exposure by 97-99%[32]. The annual average dose received by workers exposed to radiation should be between 1-5 mSv. When fluoroscopy machine operators use radiation protection methods, their radiation dose can be limited to <1 mSv per year. Notably, each dose can have a harmful effect. Hence, most doctors believe that even a single radiological X-ray carries a small risk. Therefore, the ALARA principle is accepted as the gold standard in radiology practice.

The dose area product (DAP) and kerma area product (KAP) are radiation dose monitoring methods used in radiographic and fluoroscopic studies. They provide indications of the radiation dose received by a patient. DAP is calculated as the product of the dose and beam area (Gy/cm^2). It can be divided by the area of exposure (cm^2) to determine the event total exposure (air kerma) of that area, which can be used to calculate the skin's accumulated dose. It is important to measure this in interventional and fluoroscopic procedures because of the risk of deterministic effects.

In a previous study involving 228 patients, KAP and fluoroscopy time (FT) were recorded in 47 patients to whom lumbosacral ESI was administered. It was found that the longer the fluoroscopy period, the longer was the KAP in both transforaminal and caudal ESIs. FT was longer for transforaminal than for caudal ESIs. However, the KAP of transforaminal ESI was less than that of caudal ESI after correction for the length of FT[33].

Kim et al.[34] evaluated radiation exposure and response time during various ESI procedures (caudal, interlaminar, and transforaminal) according to surgical seniority (senior faculty, junior faculty, and trainee) and fluoroscopy type [continuous monitoring (CM) or intermittent monitoring (IM)]. DAP, FT, and intervention time during lumbar ESI were compared. Radiation exposure was found to be within the established safety limits during lumbar ESIs under CM, depending on practitioners and methods. With an experienced practitioner, IM resulted in less radiation exposure than CM. IM is reported to be effective at reducing radiation exposure and appears to be preferable to CM.

Cushman et al.[35] studied the relationship among BMI, FT, and radiation dose during lumbar ESI and found that fluoroscopy radiation dose and FT during lumbar ESIs increased in older patients and those with a high BMI; the presence of a trainee did not affect FT. The present study found no difference in terms of BMI between the two experimental groups.

Tecer et al.[36] investigated differences in the radiation exposure of patients between the oblique and posteroanterior views. Data regarding the total KAP, procedure duration, and FT were obtained from medical records. The authors concluded that radiation risk does not vary between these approaches.

A previous study found that the duration of fluoroscopy exposure (for various interventional procedures) in educational settings such as university hospitals is significantly higher than in private practice settings. Significant differences were also found among physicians in the same university setting[37].

Hwang et al.[38] conducted a study to predict and compare the radiation exposure of patients during transforaminal fluoroscopy-guided ESI at different vertebral levels. The patients were categorized into three groups according to the injected lumbosacral nerve level (L2-L4, L5, or S1); FT and DAP were recorded. After correcting for FT, DAP was found to be significantly lower at S1 than that at either L2-L4 or L5.

When there is direct physician control of the fluoroscopy unit in fluoroscopy-guided lumbar spinal interventions, the FT required is significantly shorter (6 seconds), which results in a lower radiation dose (DAP, 0.59 Gy·cm^2)[39].

A previous study compared the safety of reducing radiation exposure via high-dose CM fluoroscopy, medium-dose pulsed fluoroscopy (eight pulses per second), and low-dose pulsed fluoroscopy (one pulse per second) in 231 patients receiving

Braun lumbar transforaminal ESI. Pulsed fluoroscopy reduced the radiation dose by up to 72.1% without causing any significant adverse events; thus, it should be considered the initial fluoroscopic for reducing radiation exposure[40]. In our study, we used pulsed fluoroscopy to reduce radiation exposure. The use of ultrasound guidance reduced the number of fluoroscopy shots administered by approximately 80%.

Approximately 250-300 deaths occur per year in the United Kingdom due to cancer arising directly from medical radiation exposure[41].

A study by Botwin et al.[42] found that the physician's radiation exposure is within safety limits when appropriate techniques are used. In our study, we used a lead apron during CESI in the classical fluoroscopic group. In the ultrasound guidance-assisted group, fluoroscopy was used only to confirm that the needle was in the caudal canal; all personnel in the operating room were protected from the fluoroscopy device by maintaining a 5m distance from it or leaving the room. Because radiation exposure is cumulative over a lifetime, it is necessary to employ basic principles of radiation protection, including maximizing distance from the radiation source, using shielding materials, and minimizing exposure time. Even if protective clothing is used (e.g., lead apron, lead goggles, and radiation-attenuating gloves), the radiation hazard is still a significant concern for the radiologists who perform interventions. Regardless of the protection measures taken, it is never possible to reset radiation exposure. The most effective prevention of radiation exposure may be a reduction of the use of fluoroscopy (e.g., using ultrasonography).

Study Limitations

Although our study was limited in measuring radiation exposure by the number of fluoroscopy shots (rather than direct measurement), we consider that the radiation dose was minimal.

CONCLUSION

Modern ultrasonography enables good visualization of anatomical structures in real-time and avoids the hazards posed by radiation and iodinated contrast media. We believe that CESI with ultrasound guidance is effective for acute and chronic low back pain with the advantage of minimal radiation exposure. Long-term, follow-up and comparative studies with larger numbers of patients are required for evaluating the efficacy of CESI.

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Ethics

Ethics Committee Approval: The study was approved by the Ankara City Hospital Ethics Committee (decision no: E1/913/2020, date no: 16.07.2020).

Informed Consent: Informed written consent was obtained from all patients evaluated at an outpatient clinic.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.G., A.D., Concept: A.G., A.D., Design: A.G., A.D., Data Collection or Processing: A.G., Y.C.Ş., R.K., Analysis or Interpretation: A.G., Literature Search: A.G., Y.C.Ş., R.K., Writing: A.G.

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EFFECT OF RIGID AND HYBRID ROD ON THE DEVELOPMENT OF ADJACENT SEGMENT DISEASE AFTER LUMBAR SPINAL FUSION: OUR CLINICAL EXPERIENCE

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ABSTRACT

Objective: One of the most effective treatment methods for degenerative lumbar spine pathologies is fusion surgery. However, after fusion surgery, adjacent segment disease (ASD) status may occur. Our aim in this study was to evaluate the relationship between hybrid rod use and ASD and to contribute to the literature.

Materials and Methods: Patients who came to our clinic with various etiologies and underwent lumbar spinal fusion between January 2017 and June 2022 were examined in this study. Retrospective analysis was performed on factors, such as demographic characteristics of the patients, etiology, preoperative imaging, a type of rod used during surgery, development of ASD in the postoperative period, and reoperation.

Results: There were 53.5% (n=85) female cases and 46.5% (n=74) male cases. In all cases, the mean age was 59.5 years (38-69). In group A (n=72), which used a rigid rod, 54.2% (n=39) of the cases were female, and 45.8% (n=33) were male. There were 58 patients in this group who had three or fewer levels of fusion. Group B (n=87), which used a hybrid rod, had 52.9% (n=46) female cases, and 47.1% (n=41) premature cases. Radiographically, ASD was found in 48.6% (n=35) of group A patients. Because they were symptomatic, 45.7% (n=16) of these cases were reoperated. Radiographically, ASD was found in 25.3% (n=22) of group B patients. Because they were symptomatic, 18.2% (n=4) of these cases were reoperated. Patients with rigid rods were more likely to develop ASD, and they required more reoperations ($p<0.05$).

Conclusion: Patients who undergo degenerative lumbar region fusion surgeries with hybrid rods have less ASD. As more mobile instrumentation techniques are developed in the upper segments, the incidence of ASD in these fusion surgeries will decrease.

Keywords: Adjacent segment disease, hybrid rod, lumbar fusion, rigid rod

INTRODUCTION

Fusion surgery remains the gold standard treatment method for degenerative lumbar pathologies characterized by instability[1-5]. Instability, trauma, infection, tumor, collapse fracture, spinal canal stenosis, degenerative spondylolisthesis, scoliosis, degenerative disc disease, facet syndromes, and pseudoarthrosis are treated with spinal fusion[6,7].

Adjacent segment disease (ASD) can develop after lumbar spinal degenerative spine decompression and fusion surgery[8-12]. It is believed that biomechanical changes at the operated level and adjacent segments play a role in the onset of ASD after decompression surgery[13-18]. These biomechanical changes are attributed to factors, such as spinal column stress, excessive movement, increased intra-disc pressure, and posterior displacement of the axis of motion[19-23]. Age, sex, obesity, postmenopausal status, osteoporosis, spinal stenosis, pre-existing degenerated disc at the adjacent level, fusion length, rigid pedicle screw instrumentation, and injury to the facet joint of the adjacent segment are also blamed in the etiology[15,19,24,25]. The risk of ASD is generally highest in the upper adjacent region[26]. The annual rate of surgical intervention for ASD after fusion has been reported to be 3.9%, with a range of 25-35% after 10 yr[3].

This study aims to evaluate our data on ASD in patients who had spinal fusion with rigid and hybrid rods in our clinic to the literature.

MATERIALS AND METHODS

Patient Population

Patients who applied to our clinic with various etiologies and underwent lumbar spinal fusion between January 2017 and June 2022 were examined in this study. Factors, such as demographic characteristics of the patients, etiology, preoperative imaging, type of rod used during surgery, postoperative ASD development, and reoperation, were studied retrospectively.

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The study included patients aged 38-69 yr who underwent lumbar spinal fusion in our clinic. The studies excluded cases in which lumbar cage and interbody fusion material were used during lumbar spinal fusion.

From the patient files of 159 patients, factors, such as mean age, gender, operation level, ASD development, reoperation, and follow-up time after the first surgery were collected. The patients were divided into two groups for evaluation (A and B). The rigid rod was used by group A, and the hybrid rod was used by group B.

Approval was obtained for the study from University of Health Sciences Turkey, Gülhane Scientific Research Ethics Committee for in this retrospective study (decision no: 2021-238, date no: 20.05.2021).

Radiological Evaluation

Preoperative lumbar magnetic resonance imaging (MRI) and lumbar computed tomography (CT) examinations were used to determine the pathological level in all cases. In all cases, lumbar CT was performed in the early postoperative period to assess screw malposition.

MRI was performed in the postoperative follow-up, and instability, disc herniation, disc bulging and canal stenosis were evaluated as ASD findings.

RESULTS

There were 53.5% (n=85) female cases and 46.5% (n=74) male cases. In all cases, the mean age was 59.5 yr (38-69). Group A (n=72) used a rigid rod, and 54.2% (n=39) of the cases were female, whereas 45.8% (n=33) were male. There were 58 patients in this group who had three or fewer levels of fusion. In group B (n = 87), which used a hybrid rod, 52.9% (n=46) of the cases were female, whereas 47.1% (n=41) were male. In this group, 82 patients had three or fewer levels of fusion. Demographic factors and other clinical parameters of the cases are summarized in Table 1.

ASD was found on radiographs in 48.6% (n=35) of the patients in group A, (Figure 1). There were 45.7% (n=16) cases reoperated because they were symptomatic. In this group, the mean follow-up time from the first operation was 50.2 months (12-62).

ASD was found on radiographs in 25.3% (n=22) of the patients in group B, (Figure 2). There were 18.2% (n=4) cases reoperated because they were symptomatic. In this group, the mean follow-up time from the first operation was 56.5 months (15-61).

ASD developed above the fusion level in all cases. In patients who underwent reoperation, the fusion level was extended by ascending to an upper segment including the adjacent segment. Because the rods had to be removed to prolong the fusion level, the hybrid rod was used in cases where rigid rods were inserted.

Statistical Analysis

IBM SPSS Version 25.0 for data analysis (IBM Corp., Armonk, NY) statistical package program was used. Categorized variables were explained as the number of patients (n) and percentage (%) with descriptive statistics. The relationship between categorical data in independent groups was examined with the chi-square (χ^2) test. Differences at the $p<0.05$ level were considered statistically significant.

The relationship between patient groups and development of ASD is shown in Table 2. There is a statistically significant difference between the development of ASD and the instrumentation method (p=0.002). ASD developed more frequently in patients with rigid rods.

The relationship between patient groups and reoperation is shown in Table 3. There is a statistically significant difference between the reoperation situation and the instrumentation method (p=0.001). The need for reoperation developed more frequently in patients with rigid rods.

DISCUSSION

Spinal decompression and fusion surgery are common treatments for degenerative lumbar pathologies[27-29]. However, after lumbar fusion, there may be hypermobility in the proximal adjacent segments and a decrease in disc height. As a result, ASD may develop[30,31].

Radiologically, ASD is common but may not always be symptomatic. In a review that included many studies, it was reported that the incidence of ASD radiologically varied between 8% and 100%, whereas the incidence of symptomatically varied between 5.2% and 18.5%[25].

Table 1. Demographic and clinical characteristics of the cases

Characteristic		Group A (n, %)	Group B (n, %)
Number of patients		72	87
Average age		60.8	58.3
Sex	Female	39 (54.1)	46 (52.8)
	Male	33 (45.8)	41 (47.1)
Fusion level	≤3	58 (80.5)	82 (94.2)
	>3	14 (19.4)	5 (5.7)
Adjacent segment disease		35 (48.6)	22 (25.3)
Reoperation		16 (45.7)	4 (18.1)
Follow-up (month)		50.2	56.5

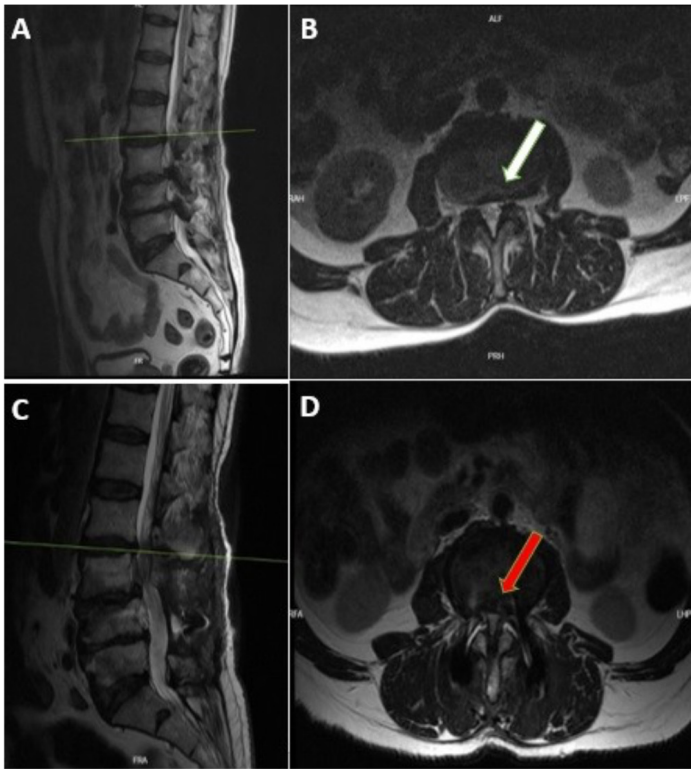

Figure 1. **A** and **B**, preoperative sagittal and axial lumbar T2 MRI. A 58-year-old male patient underwent lumbar decompression and fusion surgery for L3-L5 spinal stenosis. **C** and **D**, postoperative sagittal and axial lumbar T2 MRI. A rigid rod was used during the operation. Lumbar MR imaging performed on the patient's leg pain and neurogenic claudication complaints at the postoperative 15th month revealed adjacent segment disease at the L2-L3 level. The patient was reoperated. White arrow: Canal diameter at L2-L3 level in the preoperative period. Red arrow: Canal diameter at L2-L3 level in the postoperative period.
MRI: Magnetic resonance imaging

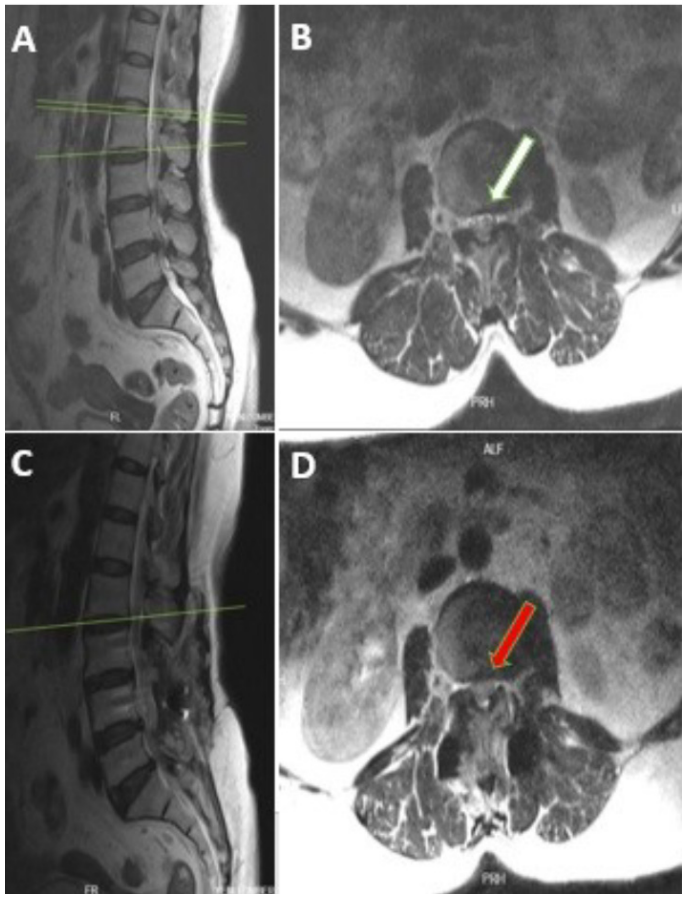

Figure 2. **A** and **B**, preoperative sagittal and axial lumbar T2 MRI. A 63-year-old female patient underwent lumbar decompression and fusion surgery for L3-L5 spinal stenosis. **C** and **D**, postoperative sagittal and axial lumbar T2 MRI. A hybrid rod was used during the operation. The patient presented with mild low back pain at the postoperative 18th month. In the lumbar MRI, there was no apparent adjacent segment disease in the upper segments. White arrow: Canal diameter at L2-L3 level in the preoperative period. Red arrow: Canal diameter at L2-L3 level in the postoperative period.
MRI: Magnetic resonance imaging

Because the lumbar region contains five mobile segments, when any segment joins the fusion, loading in adjacent segment areas increases. Therefore, fusion surgery accelerates the progression of degenerative changes in adjacent segments[23]. When the effects of anterior and posterior fusion surgery on ASD were compared, posterior fusion surgery was found to have a higher rate of ASD than anterior (44% and 82.6%, respectively)[32]. The cause of this is disruption of the posterior ligament system at the level of the adjacent segment, which accelerates the existing degenerative process[33]. Cunningham et al.[9] demonstrated that rigid instrumentation resulted in a 45% increase in axial compressive and flexion loads in upper adjacent disc tissue.

Kumar et al.[34] reported that the most common cause of radiological ASD is retrolisthesis. On the other hand, Min et al.[35] blamed the most common angular instability in the etiology. Other factors implicated in the etiology are disc degeneration, hypertrophic facet joint arthritis, widespread degeneration and weakness of the paraspinal muscles, nucleus pulposus herniation, and stenosis[19,25,30]. It has also been reported that loss of lumbar segmental lordosis has an effect on the development of ASD[36,37]. Age is an important factor in etiology, and the probability of ASD is higher in fusions over 55 yr of age. Due to age-related widespread deterioration, the resistance of the adjacent segment to increasing stress decreases after fusion[27,38,39]. In our study, the mean age of all cases was evaluated as 59.5 yr.

Kim et al.[37] retrospectively evaluated 69 patients who had L4-L5 fusion for lumbar stenosis or degenerative spondylolisthesis. They concluded that maintaining 20° or more segmental lordosis is important in preventing ASD[37]. Bae et al.[36] reported similar results. Anandjiwala et al.[40] found that pre-existing adjacent segment degeneration, rather than postoperative balance, was a risk factor for radiological ASD in a 5yr prospective follow-up after lumbar spinal fusion. Other studies have found that the incidence of adjacent segment degeneration increases with the number of fusion levels and that there is a significant correlation between patient clinical outcomes and the number of fusion levels[24,41].

Correlation studies between clinical manifestations of ASD and

Table 2. Development of adjacent segment disease according to patient groups

	Adjacent segment disease		
Patient group	+ (n=57)	- (n=102)	p value
Group A (n=72)	35 (48.6%)	37 (51.4%)	0.002
Group B (n=87)	22 (25.3%)	65 (74.7%)	
Pearson chi-square test, p<0.05			

Table 3. Reoperation relationship according to patient groups

	Reoperation		
Patient group	+ (n=20)	- (n=139)	p value
Group A (n=72)	16 (22.2%)	56 (77.8%)	0.001
Group B (n=87)	4 (4.6%)	83 (95.4%)	
Pearson chi-square test, p<0.05			

radiological findings are discussed separately. There are many studies in this area. Boden et al.[42] discovered that although ASD findings were seen on lumbar MRI, approximately 57% of patients aged 60 yr and older did not have clinical symptoms. Disc degeneration or disc bulging was observed at a rate of 35% in radiological examinations of healthy young adults aged 20 to 39[42]. The rate of radiologically detected ASD in our study was 35.8%, whereas the rate of symptomatic ASD was 12.5% in all cases.

During fusion in the lumbar spine, hybrid stabilization is utilized by using a dynamic rod in the proximal segment and a rigid rod in the distal segments. Unlike the posterior rigid stabilization technique, the posterior hybrid stabilization technique carries the load applied to the spine. The load is not shared with the spine in the rigid system[43]. The instrumented segments in the rigid system are motionless and behave like long bones. Therefore, the spine increases motion in the adjacent segments of the instrumented segments to reach its natural range of motion, causing an increase in load in the adjacent segments[11]. The significant difference in loading (stress) between the instrumented segment and the adjacent non-instrumented segment allows deformity to develop[44].

In recent years, posterior dynamic stabilization techniques have been used to treat spinal deformities with chronic instability. In this regard, Graf[27], who coined the term "dynamic artificial ligament", was the first to use it in the treatment of degenerative disc disease in 1992. Schwarzenbach et al.[45] found a statistically significant improvement in both fusion development and clinical complaints after a mean follow-up of 39 months in 31 patients who used a hybrid system for degenerative disc disease. While the rate of symptomatic ASD in our cases with dynamic stabilization using a hybrid system rod was 25.3%, the rate of symptomatic KSH in cases with rigid rod was 48.6%. When the hybrid system rod was used, statistically less KSH developed compared with the rigid system, and there was less reoperation (p<0.05).

Study Limitations

Our research has some limitations. The first is the small number of cases. Second, because it is a retrospective study, the data were analyzed over the files, and the unsaved data of the patients could not be accessed.

CONCLUSION

In degenerative lumbar spine pathologies, fusion surgery is still an effective treatment method. However, due to different factors, ASD occurs due to biomechanical stress, particularly in the upper segment where the fusion ends. This biomechanical stress and ASD are reduced when hybrid or dynamic rods are used instead of rigid rods. With the advancement of rod and other instrumentation techniques, it is expected that postoperative ASD will be reduced even further in the future.

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Ethics

Ethics Committee Approval: Approval was obtained for the study from University of Health Sciences Turkey, Gülhane Scientific Research Ethics Committee for in this retrospective study (decision no: 2021-238, date no: 20.05.2021).
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Authorship Contributions

Surgical and Medical Practices: İ.G., A.D., Concept: A.D., H.T., Design: İ.G., A.D., Data Collection or Processing: A.D., H.T., M.O.D., Analysis or Interpretation: İ.G., A.D., Literature Search: A.D., M.O.D., Writing: A.D., M.O.D.
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RETROSPECTIVE OBSERVATIONAL STUDY OF PARAVERTEBRAL INTRAMUSCULAR OZONE/OXYGEN INJECTION IN THE TREATMENT OF CHRONIC NONSPECIFIC LOW BACK PAIN

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ABSTRACT

Objective: Chronic non-specific low back pain is a very common musculoskeletal condition that affects the quality of life. It is critical to be treated with effective, safe and minimally invasive treatments. In this study, we analyzed the impact of paravertebral ozone/oxygen (O_3/O_2) treatment injection treatment on distress and disability in patients with chronic non-specific low back pain.

Materials and Methods: From January 2019 to December 2021, 426 patients who underwent paravertebral ozone injections due to low back pain were examined retrospectively; 305 patients who met the study criteria were included. The patients were injected with 15 Î¼g (50 mL) O_3/O_2 gas in the paravertebral muscle. Paravertebral O_3/O_2 injections were administered once a week for 5 weeks. Visual analog scale (VAS)-resting, VAS-activity and Istanbul Low Back Pain Disability Index (ILBPDI) were recorded at pre-treatment, post-treatment, and 6-month follow-ups.

Results: Of the patients included in the study, 158 (51.8%) were female, 147 (48.2%) were male and the mean age of all patients was 45.6±8.8.VAS-resting, VAS-activity decreased statistically significantly after treatment and 6 months after treatment compared to pretreatment ($p<0.001$). The mean ILBPDI score of the patients decreased statistically significantly after the treatment and at the 3rd month and 6th month after the treatment compared with the pre-treatment ($p<0.001$). There was no significant difference between the post-treatment and post-treatment 6-month measurements.

Conclusion: In our study, it was found that paravertebral O_3/O_2 therapy for treating chronic nonspecific low back pain was effective in improving pain, functional status and activities of daily living, and its effect continued in the long term.

Keywords: Non-specific low back pain, paravertebral ozone, intramuscular ozone, disability

INTRODUCTION

Chronic non-specific low back pain (CNLBP) is defined as low back pain lasting longer than 12 weeks, not due to a clearly defined anatomical or physiological cause[1]. Often, a specific pathology such as infection, tumor, fracture, or inflammatory disease that cause low back pain cannot be detected, and nonspecific low back pain is diagnosed in 80-90% of the cases[2,3]. It is known in many clinical studies that chronic nonspecific low back pain, which has been shown to cause not only nociceptive but also neuropathic pain, adversely affects functionality, social participation, and mental and financial well-being. Although most of the resources are allocated for the treatment of chronic low back pain, the success rate of treatment is low. For this reason, it is extremely important to investigate more effective methods for coping with chronic low back pain to improve the health and quality of life of patients[2-6].

Especially the ineffectiveness of medical applications (with paracetamol, nonsteroidal anti-inflammatory drugs, and myorelaxant) in the treatment of chronic nonspecific low back pain has led to different treatment searches[5,6]. Therefore, it is of great importance to treat chronic nonspecific low back pain with safe and practical minimally invasive techniques. Ozone/oxygen (O_3/O_2) gas therapy applied to the paravertebral muscles is a practical, safe and easy mini-invasive technique[7]. Multiple mechanisms of action have been demonstrated to explain the efficacy of ozone therapy, including analgesic, anti-inflammatory, and oxidant action on proteoglycans (eg in the nucleus pulposus)[8]. Ozone rapidly transforms into molecular oxygen and oxygen radicals in biological environments, creating a moderate oxidative stress in the body. In this way, ozone is perceived as an oxidative threat in the body. This results in the stimulation of enzymes working in antioxidant defense systems.

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The ozone dose should be sufficient to produce an acute, clear and temporary oxidative stress. Lower doses cause a placebo effect, while higher doses cause toxicity[9]. Therefore, it is very important to set ozone doses correctly. Moderate oxidative stress activates nuclear factor-erythroid 2-related factor-2 (Nrf2). Nrf2 triggers the transcription of antioxidant response elements. However, severe oxidative stress causes an inflammatory response by activating nuclear transcription factor kappa, resulting in tissue destruction by increasing cyclooxygenase-2, prostaglandin E2 and cytokine production[10]. The key point in ozone therapy is the regulation of oxidative stress level.

Many studies examining the efficacy responses of specific low back problems with paravertebral ozone therapy have been found, but no study has been found on paravertebral ozone therapy in patients with chronic non-specific low back pain. Accordingly, our study aimed to determine the effects of paravertebral O_3/O_2 therapy (OOT) on pain, functionality, and activities of daily living in patients with chronic nonspecific low back pain.

MATERIALS AND METHODS

A total of patients were analyzed retrospectively in this study. The study protocol was approved by the Yeditepe University Faculty of Medicine Ethics Committee (decision no: 2022/001, date: 09.06.2022). The registration number for the study is 2022/001. The study was conducted following the principles of the Declaration of Helsinki.

Study Design

Patients with CNLBP who had low back pain for at least 3 months and were administered paravertebral O_3/O_2 injection in the anamnesis of the patients who applied with the complaint of low back pain between January 2019 and December 2021 were included in the retrospective study. Patients diagnosed with nonspecific low back pain by a physiatrist according to magnetic resonance imaging findings and without radicular leg pain were included in the study.

Inclusion criteria for the study were: Being between the ages of 25 and 65, having nonspecific low back pain lasting longer than 3 months that did not respond to conventional conservative treatment methods, having a visual analog scale (VAS) score of 4 or higher in VAS evaluation and not be included in any other treatment for chronic low back pain during the study.

Exclusion criteria: Presence of a specific cause of low back pain such as lumbar spinal stenosis, radiculopathy, cancer, inflammatory arthritis, history of previous spinal surgery, presence of pathological findings in neurological examination (loss of sensation in lower extremities, loss of position sense, loss of motor muscle strength), severe cardiovascular or respiratory system pathologies, uncontrolled diabetes mellitus, unhealed fracture or open surgical wound, and the application of algological interventional treatment to the lumbar region in the last 6 months.

Treatment Procedure

All patients were treated with injections using the same medical ozone generator (Salutem model, İstanbul, Turkey). Injections were made into the paravertebral muscles using a 13 mm injector tip, with a total of 15 µg/mL in 50 mL of O_3/O_2 gas administered through ozone-resistant injectors. Paravertebral O_3/O_2 injections were administered once a week for 5 weeks.

While the patient is standing, the spinous process point which is the midpoint of the imaginary line passing over the crista iliacas in the lumbar region is determined as the L4 vertebra spinous process. The upper and lower spinous processes are then marked by palpation. The area is cleaned with alcohol and O_3/O_2 is injected vertically 2 cm above and below the spinous processes, starting 1 cm lateral to the spinous process, while the patient is in the prone position. The 21 gauge injector tip was applied at a depth of 3 cm. A total of 4 injections were applied to the paravertebral muscles at the level of L4 and L5 vertebrae bilaterally and no premedication or anesthesia was given. All paravertebral ozone applications were performed by an experienced specialist physician and all sessions were performed by the same person.

Before starting the treatment program, lumbar isometric exercises (pelvic tilt exercises, hamstring stretching, and modified straightening) were shown to all patients by the same physiotherapist and they were told that these exercises should be performed for 20 minutes a day, at least 5 days a week.

Evaluation Measures

VAS-resting, VAS-activity, and Istanbul Low Back Pain Disability Index (ILBPDI) were recorded at pre-treatment, post-treatment, and 6-month follow-ups.

Pain intensity was measured using the VAS. The patients were asked to rate their pain intensity on the scale by explaining what the numbers meant on a 10 cm-long horizontal line. Zero means no pain, and 10 means severe pain. The pain intensity of the participants was defined in 3 situations: At rest, during forward bending, and backward stretching movements. The point marked by the participants on the line was measured with a ruler, and the VAS value was recorded in cm[11].

ILBPDI, which evaluates functional status, is a specific scale developed for the evaluation of patients with chronic low back pain. ILBPDI contains 18 questions, each question is scored with a 6-point (0-5 points) Likert scale. The questions relate to the patients' activities of daily living during the past month. Total scores range from 0 to 90, with higher scores indicating greater disability. A validity and reliability study of ILBPDI was conducted[12]. The scores of the patients were made by a physiatrist who did not administer ozone injection.

Statistical Analysis

The data of the study were analyzed using the IBM SPSS Statistics 22 (IBM SPSS, Armonk, NY, U.S.A.) program, and $p<0.05$ was accepted as the significance level. In summarizing the data obtained from the study, descriptive statistics were tabulated as mean ± standard deviation or median, minimum and maximum depending on the distribution of continuous numerical variables. Pre- and post-injection data were compared using the one-way ANOVA test for repeated measures.

RESULTS

Four hundred twenty six patients who underwent paravertebral ozone injections due to low back pain were examined retrospectively; 305 patients who met the study criteria were included. Of the patients included in the study, 158 (51.8%) were female, 147 (48.2%) were male and the mean age of all patients was 45.6±8.8 years, the mean body mass index was 26.4±5.5 kg/m^2 and 132 patients smoked. Of the patients, 190 (62.2%) were working in a paid job and 106 (34.7%) had primary education. The mean duration of low back pain in the patients was calculated as 32±9.9 months. While the duration of symptoms was 12 months or less in 31.8% (n=97) of the patients, the duration of low back pain was over 12 months in 68.2% (n=208) of the patients. Table 1 shows the sociodemographic and clinical characteristics of the patients. According to the information determined from the recorded file data, no complications were observed during the injection. Post-injection pain and stiffness were observed in 154 patients within the first three days, after which it was reported that the symptoms regressed.

VAS-resting, VAS-activity decreased statistically significantly after treatment and 6 months after treatment compared to pretreatment ($p<0.001$). The mean ILBPDI score of the patients decreased statistically significantly after the treatment and 6th month after the treatment compared to the pre-treatment ($p<0.001$). The changes in the evaluation criteria before and after the treatment are shown in Table 2.

According to the pairwise comparisons of the evaluation criteria, statistical significance was found in all parameters when pre-treatment and post-treatment, and pre-treatment and post-treatment 6 months were compared ($p<0.05$). There was no significant difference between the post-treatment and post-treatment 6-month measurements. Pairwise comparisons of the evaluation criteria with the measurements made before and after the treatment are shown in Table 3.

DISCUSSION

In a global systematic study conducted in 2012, the point prevalence of chronic nonspecific low back pain in the adult population was 12%, and the lifetime prevalence was as high as 40%. The aim of the treatment of chronic non-specific low back pain is to relieve pain, restore function and prevent recurrence[13]. It is known that chronic low back pain is often not treated appropriately. Therefore, it is very important to determine the effectiveness of new, effective, and reliable treatment methods. Minimally invasive treatment methods have been developed (such as corticosteroid and anesthetic injections, acupuncture, mesotherapy, and platelet-rich plasma injection) in addition to physiotherapy and vertebral manipulation to treat chronic low back pain.

Ozone; it is a molecule formed by the coexistence of 3 oxygen atoms, and it is a treatment method that provides treatment for many diseases with wide application areas and low incidence of side effects. Paravertebral OOT is a treatment method that has become widespread and has direct and indirect mechanical and anti-inflammatory dual effects[14,15]. Dissolved ozone in body fluids reacts immediately with antioxidants and polyunsaturated fatty acids, resulting in rapid-acting reactive oxygen compounds [most importantly hydrogen peroxide (H_2O_2)] and lipid peroxidation products with longer half-lives[9]. In the first phase, H_2O_2 diffuses into the cell cytoplasm and acts as a trigger. It causes different chemical pathways according to the cell types it affects. Reactive oxygen products act as short-acting messengers and are removed by antioxidants in a very short time, but the complex pharmacodynamics of lipid peroxidase products allow them to be long-term messengers by minimizing their potential toxicity[10]. It is a less stable molecule than oxygen, it has a more biological response and blocks the phospholipase A2 enzyme, and suppresses inflammation[15].

Table 1. Sociodemographic and clinical characteristics of the patients

Variables	Mean ± SD (%)	Median (minimum-maximum)
Age	45.6±8.8	46.0 (29-63)
Gender (%)		
Female	158 (51.8%)	
Male	147(48.2%)	
BMI (kg/m)	26.4±5.5	26 (18.4-37.5)
Working condition (%)		
Working in paid job	190 (62.2%)	
Not working	115 (37.8%)	
Education (%)		
Primary education	106 (34.7%)	
High school	89 (29.1%)	
University	76 (24.9%)	
Graduate	34 (11.1%)	
Low back pain duration (months)	32±9.9	25.5 (6.0-45.5)

SD: Standard deviation, BMI: Body mass index

Table 2. Comparison of the evaluation criteria before treatment, after treatment, and 6 months after treatment

	Before treatment	After treatment	6 months after treatment	p values
VAS-resting	4.53±5.32 4 (0-9)	1.85±1.86 1 (0-5)	1.47±1.63 1 (0-5)	<0.001
VAS-activity	6.74±1.86 7 (3-9)	3.44±2.19 5 (0-8)	3.29±2.08 3 (0-8)	<0.001
ILBPDI	26.74±12.25 24 (8-42)	17.53±10.18 15 (0-33)	12.12±11.78 4 (0-45)	<0.001

VAS: Visual analog scale, ILBPDI: Istanbul Low Back Pain Disability Index

Table 3. Paired comparisons of assessment criteria before and after treatment and 6 months after treatment

	VAS-resting p	VAS-activity p	ILBPDI p
Before treatment-after treatment	<0.001	<0.001	<0.001
Before treatment-6 months after treatment	<0.001	<0.001	<0.001
After treatment-6 months after treatment	0.723	0.489	0.367

VAS: Visual analog scale, ILBPDI: Istanbul Low Back Pain Disability Index

Cantele et al.[16] reported that intramuscular paravertebral O_3/O_2 injections in 21 patients with chronic low back pain improved their pain and disability outcomes, along with a better outcome in psychological well-being due to lumbar low back pain.

In a systematic review that included 15 studies examining 2,597 patients in total, it was stated that OOT was effective in pain control and functional improvement. However, looking at the quality of the literature, none of the included studies reached the standard of "good quality", 3 were rated as "moderate" and the rest were rated as "poor"[17].

Lumbar paravertebral O_3/O_2 injections in the treatment of low back pain are minimally invasive, safe, cheaper, and effective in relieving pain as well as disability. It has been reported in the literature that only a very small proportion of patients have non-serious side effects. This technique is easy to apply and does not require premedication, CT, or surgery environment, it is an injection that can be done safely in outpatient clinic conditions[15]. In our study, it has been shown that paravertebral OOT is effective on pain, activities of daily living, and disability in patients with chronic nonspecific low back pain.

Patients with low back pain for at least 6 months who had previously received medical and physical therapy but did not benefit were included in our study. Therefore, when evaluating the results of our study, it should be taken into account that the pain of the patients is chronic and resistant. However, it is seen that the patient population is similar in the studies conducted[16-18].

Study Limitations

Limitations of this study include its retrospective design, absence of a control group, and lack of power analysis. Our results show that paravertebral ozone injections are a safe and easy treatment that is minimally invasive for patients with chronic nonspecific low back pain. There are not enough studies on this treatment method. More prospective randomized and controlled studies are needed to increase the safety of paravertebral injection therapy.

CONCLUSION

In our study, it was found that paravertebral OOT in the treatment of chronic nonspecific low back pain was effective in improving pain, functional status, and activities of daily living, and its effect continued in the long term. It is thought that paravertebral OOT can be recommended as an effective and safe treatment option in patients with CNLBP with appropriate indications. There is a need for randomized controlled studies with more patients.

Ethics

Ethics Committee Approval: The study protocol was approved by the Yeditepe University Faculty of Medicine Ethics Committee (decision no: 2022/0001, date: 09.06.2022).

Informed Consent: Informed consent was obtained from all patients before injection.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: S.K., I.F.K., Design: S.K., I.F.K., Data Collection or Processing: S.K., Analysis or Interpretation: S.K., I.F.K., Literature Search: S.K., I.F.K., Writing: S.K., I.F.K.

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EFFECT OF MESENCHYMAL STEM CELL AND ERYTHROPOIETIN COMBINATION IN A RAT SPINAL FUSION MODEL

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ABSTRACT

Objective: The benefits of erythropoietin (EPO) or mesenchymal stem cell (MSC) application during spinal fusion were discussed in the literature. Still, the effect of the combination may enhance favorable outcomes. This study compared the efficacy of MSCs and EPO treatments separately and together in a rat model.

Materials and Methods: This study was designed as an experimental, controlled animal study. The groups consisted of EPO or MSC application or both: PreS - EPO + MSC (EPO starting 24 h before the surgery) or PostS - EPO + MSC (EPO starting 72 h after the surgery) with control groups. Experimental posterolateral L4-L5 spinal fusion was performed. Plain radiographs and multi-detector computed tomography scans were performed for the rats preoperatively and at the 3rd and 6th weeks. Using the Mimics Innovation Suite, 3D models of the fusion site were reconstructed, volume analysis and volumetric changes in these periods were calculated. Manuel palpation assessment and histopathological analyses were also performed to assess the fusion.

Results: Radiologically, the fusion rate at weeks 3 and 6 were significantly higher in the EPO + MSC groups than that in the EPO group alone. The highest bone-volume increase was detected in the PostS - EPO + MSC groups. The PreS - EPO + MSC-3 group and the PostS - EPO + MSC-6 group had the highest fusion rates according to manual palpation (p=0.048, 71.4%). The EPO groups had lower fusion rates compared to those in the control and MSC groups (14.3 % both at the 3rd and 6th weeks). The PreS - EPO + MSC-3 group had the highest histological score among the groups. The EPO-6 and PostS - EPO + MSC-6 groups had the lowest scores with respect to histological examination.

Conclusion: The combination of EPO + MSC application showed additionally significant benefits according to radiological and histological examination, but EPO adversely affected the fusion.

Keywords: Sprague-Dawley rat, spinal fusion, erythropoietin, mesenchymal stem cell, MDCT, Mimics Innovation Suite

INTRODUCTION

Spinal fusion or spinal arthrodesis is a widely accepted and preferred surgical treatment for various spinal diseases. The risk of pseudarthrosis or nonunion is reported to be as high as 30% after spinal fusion, which is most likely caused by the procedure or approach used and patient-related factors such as osteoporosis, health status, and comorbidities[1,2]. For achieving a stable spine segment, and to increase the rate of complete fusion, autogenous bone grafts are held to be the gold standard, but alternative treatments have been explored due to the limited amount of grafts and donor site morbidity[3-5]. Mesenchymal stem cells (MSCs) have the potential to differentiate into osteoblasts and chondrocytes, so it was proposed as a reasonable option for utilization in spinal fusion[6,7]. In various studies, MSCs has been reported to increase the success in posterolateral spinal fusion with different scaffolds[8-17]. While there is a degree of consensus with respect to the benefits of MSCs, the therapeutic expectation did not occur as completely successful[2,18].

Erythropoietin (EPO) was formerly used in spinal surgery to reduce perioperative blood transfusion as a blood conservation therapy[19,20]. Rölfing et al.[21] first showed a significant enhancing effect of EPO on bone volume in a rodent spinal fusion model. Current reviews support the role of exogenous EPO during the signaling in bone remodeling and repair *in vivo* with increased osteogenesis, osteoclastogenesis, and angiogenesis. Controversially, the stimulatory effect of EPO on osteoclastogenesis and the stimulation of bone-resorbing activity *in vitro* (concentrations >100 mU/mL) are also widely accepted[22,23].

Simultaneous or sequential application of different growth factors has been considered to deliver the synergistic effect

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in spinal fusion. There is no experimental study (*in vitro* or *in vivo*) examining the effects of the combination of MSCs and EPO on the spinal fusion model. This study aimed to compare the mechanical, radiological and histopathological efficacy of MSCs and EPO treatments separately and together in a rat spinal fusion model.

MATERIAL AND METHODS

Study Design and Animals

This study was designed as an experimental, controlled animal study. Before the study, approval was obtained from the institutional review board (Gülhane Military Medical Academy Animal Care and Use Committee, approval no: 2013/26, date: 22.11.2022). Animal care complied with the guidelines of the institution and was conducted following the Animal Research: Reporting of *In Vivo* Experiments and Guide for the Care and Use of Laboratory Animals guidelines. The studies were conducted at the same Institution's Laboratory Animals Section of the Research and Development Center. Seventy three female Sprague-Dawley rats (18-20 weeks of age) weighing 253.2±32 g were included in the study. Three rats were used for MSC production and the remaining 70 rats were randomly divided into 10 groups. Study groups were briefly designed as "only EPO application", "only MSC application", "EPO and MSC application" and "control" groups. EPO and MSC application groups were further divided into "preoperative 24-hour" and "postoperative 72-hour" sub-groups concerning the starting time of EPO administration to assess the possible anti-inflammatory effects of EPO on fusion. Other groups were divided into subgroups in the 3rd and 6th weeks according to the time of sacrification of the rats. The interventions applied and respective groups are set out in Table 1.

Allogenic Bone Marrow-Derived Mesenchymal Stem Cell Generation

Two biologists experienced in stem cell research generated the MSC using the technique of Nevruz et al.[24]. After sacrificing three rats with high-dose anesthetics, the tibia and femora of the rats were excised and bone marrow was aspirated from the medullary canal with an 18-gauge needle, collected in a centrifuge tube and diluted 1:2 with phosphate-buffered saline (PBS). In another centrifuge tube, 1:3 of the bone marrow volume was placed in Ficoll solution and the diluted bone marrow was added with a sterile pipette, layered, and then centrifuged at 1800 rpm for 30 minutes at room temperature. After centrifugation, MSCs in the middle layer were transferred to a new tube. Collected MSCs were centrifuged with 5 times the volume of PBS at least 2 times, at 1800 rpm for 5 minutes to remove the Ficoll. The cell pellet obtained at the end of the procedure was collected in a 25 cm^2 flask containing a medium consisting of 10% fetal calf serum, 6% 100 U/mL penicillin and 100 µg/mL streptomycin, and 1% L-glutamine and cultured at 37° C under 5% CO_2 pressure. Medium changes were made every 3 days. In the 7th-10th days, colonies began to form. On the 14th day, when 70% of the culture flask was covered, the cells were removed by trypsinization and placed in a 75 cm^2 flask for the 1st passage. After the 3rd passage, the cells were ready for use. To show that the passaged cells were MSCs, surface markers of CD45 (-), CD34 (-), HLA-DR (-), CD73 (+), CD90 (+), CD105 (+) were analyzed by flow cytometry.

Anesthesia Protocol

All radiological studies and surgical procedures were performed under general anesthesia. 10 mg/kg xylazine hydrochloride (Alfazyne 2%, Alfasan International B.V., Woerden, Netherlands) and 50 mg/kg ketamine hydrochloride (Brema-Ketamine 10%, Bremer Pharma, Germany) were used intraperitoneally. When necessary, 5 mg/kg xylazine hydrochloride and 10 mg/kg ketamine hydrochloride were used for maintenance.

Surgical Procedure

Experimental posterolateral L4-L5 lumbar spinal fusion was performed as previously described[25,26]. Prophylactic intraperitoneal cefazolin was administered at a dose of 22 mg/

Table 1. Characteristics of study groups

Group number	Group label	Group design
1	CT-3	Surgery, daily IP saline administration, sacrification at 3rd week
2	CT-6	Surgery, daily IP saline administration and sacrification at 6th week
3	EPO-3	Daily IP EPO starting 24 hours prior to surgery- surgery, sacrification at 3rd week
4	EPO-6	Daily IP EPO starting 24 hours prior to surgery- surgery, sacrification at 6th week
5	MSC-3	Surgery, MSC local application, IP saline, sacrification at 3rd week
6	MSC-6	Surgery, MSC local application, IP saline, sacrification at 6th week
7	PreS - EPO + MSC-3	Daily IP EPO starting 24 hours prior to surgery, surgery, MSC, sacrification at 3rd week
8	PreS - EPO + MSC-6	Daily IP EPO starting 24 hours prior to surgery, surgery, MSC, sacrification at 6th week
9	PostS - EPO + MSC-3	Surgery, MSC, daily IP EPO starting 72 hours after surgery, sacrification at 3rd week
10	PostS - EPO + MSC-6	Surgery, MSC, daily IP EPO starting 72 hours after surgery, sacrification at 6th week

IP: Intraperitoneal, Saline: 0.9% NaCl, equal to the volume of 500 IU/kg EPO dosage.
MSC application: Local application at decortication site, without osteoblastic differentiation and scaffold usage, approximately 1 million cells.
MSC: Mesenchymal stem cell, EPO: Erythropoietin, CT: Control

kg 30 minutes before the surgical incision. After the anesthesia, the lumbar region of the rats was shaved and placed in the prone position. The surgical area was cleaned with Octenisept solution (Schülke & Mayr GmbH, Norderstedt, Germany) and covered in a sterile manner. An approximately 4 cm midline skin incision between L4 and S1 was made and the lumbar fascia was opened using the Wiltse approach (Figure 1a, b, c). The paraspinal muscles were dissected laterally by blunt dissection (Figure 1d, e). The tendinous insertions of the longissimus lumborum muscles attached to the facet joints were released, revealing the L4 and L5 transverse processes (Figure 1f). The soft tissues on the transverse processes and facet joints were cleaned (Figure 1g, h). After irrigation of the surgical area with saline, the area was dried and the transverse processes, L4-L5 facet joints, laminae, and lateral surfaces of the spinous processes were decorticated using a burr at 10,000-15,000 rpm until punctate micro-hemorrhages were observed (Figure 1i, j). No further irrigation was made to preserve the bony fragments exposed during decortication. No significant bleeding was observed during the surgical procedure. In the MSC application groups, a suspension containing approximately one million MSCs, as Minamide et al.[27] suggested in their study, was applied to the decorticated area (Figure 1k) without using any scaffold. The lumbar fascia and the skin were closed (Figure 1l). In order not to trigger cannibalism, which is frequently seen in rats in the postoperative period, blood and tissue residues were cleaned from the incision area with saline. Antiseptic-disinfectant spray (Viocid®, Antiseptic Solution, Topical Spray, Provet®, Istanbul, Turkey) was applied to the incision area after the procedure.

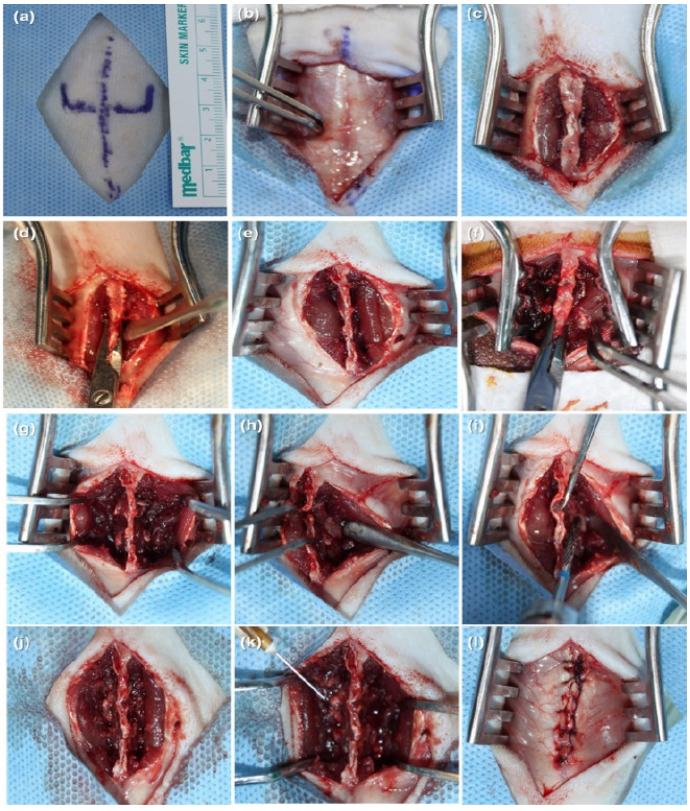

Figure 1. Posterolateral lumbar spinal fusion surgery for Sprague-Dawley rats, step-by-step procedure: Midline skin incision between L4 and S1 **(a)**. Note that marked iliac crests (caudal part of the rat) are at the top of the picture. Exposure of the lumbar fascia before **(b)** and after **(c)** the Wiltse approach. Blunt dissection **(d)** and retraction **(e)** of the paraspinal muscles. Exposure of the facet joint **(f)**. Cleaning off the soft tissues on the facet joint **(g)** and exposure of the transverse process **(h)**. Decortication of the desired fusion site using a burr **(i, j)**. Application of the mesenchymal stem cell suspension to the decorticated area **(k)**. The closure of the lumbar fascia **(l)** and the skin

Erythropoietin Administration

The EPO dose was calculated for each rat separately according to their weight. EPO alfa (Eprex; 4000 IU/mL, Santa Farma, Turkey) at a dose of 500 IU/kg/day was used intraperitoneally, as per Garcia et al.[28] in their study. To evaluate the possible anti-inflammatory effects of EPO in the inflammatory phase, which is the first stage of bone healing, the MSC and EPO groups were divided into two sub-groups, in which the EPO application started at the preoperative 24th hour (PreS - EPO + MSC groups) or postoperative 72nd hour (PostS - EPO + MSC groups). The groups that did not receive EPO were given a daily injection of saline (0.9% NaCl) in a volume equivalent to the EPO dose.

Outcome Parameters

Direct radiography: Using a digital mammography device (Selenia® Hologic, Inc. USA), a posteroanterior radiograph of the lumbar spine was taken at a dose of 30 kV 160 mAs, with a distance of 30 cm between the rat and the tube surface. Direct radiograms of the entire spine were obtained before the surgery (week 0) and at the 3rd and 6th weeks after the surgery for the designated groups. Three independent blinded observers evaluated the radiographs. For the evaluation, the commonly used criteria of Lenke et al.[29] were modified for our study. Radiographic fusion findings at the L4-L5 levels were divided into 5 stages and scored (Table 2) (Figure 2).

Computed tomography and volumetric measurement: A multidetector computed tomography (MDCT) device (Toshiba

Table 2. Modified Lenke radiological evaluation criteria used in our study

Points	Fusion status	Explanation
1	Definitely not solid	Obvious bone resorption at transverse processes bilaterally
2	Definitely not solid	No obvious fusion mass or bone resorption
3	Probably not solid	Small, thin fusion masses bilaterally
4	Possibly solid	Unilateral large fusion mass with contralateral small fusion mass
5	Definitely solid	Solid big trabeculated bilateral fusion masses

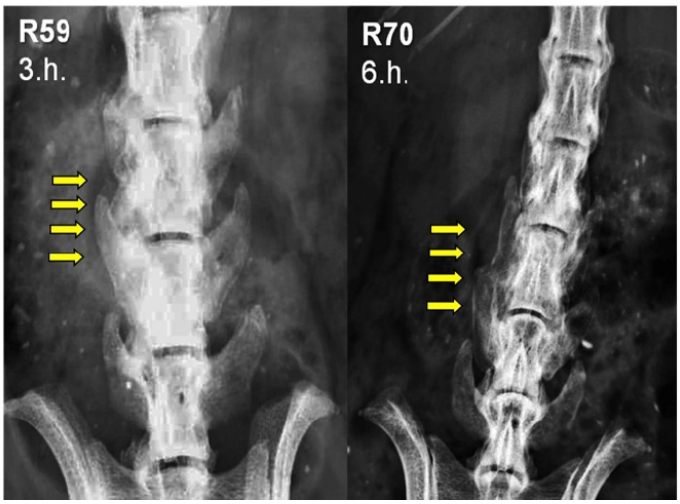

Figure 2. Direct radiography examples of two distinct rats in the third and sixth weeks that received 4 points based on our modified Lenke criteria. The new bone growth is denoted by yellow arrows

Aquilion One® 320-Detector Row CT, Toshiba Medical Systems, Tokyo, Japan) was used with a dose of 100 kVP, 200 mA for 500 milliseconds (0.5 mm slice thickness) for each rat (Figure 3). Digital Imaging and Communications in Medicine (DICOM) data were transferred to a biomedical engineering program, Mimics Innovation Suite® v16.0.0.235 (Materialise, Belgium), to reconstruct the L3-L6 segment. For all CT examinations performed at 0, 3, and 6 weeks, a 3D model was created and volume measurements were made from these models (Figures 4 and 5). The volumetric change between 0-3 weeks and 3-6 weeks was calculated for the groups.

Manual assessment of the fusion: After sacrification with high dose anesthetics at the end of the 3rd and 6th for the designated groups, the lumbar spines of the rats were en-bloc resected, and the soft tissues were stripped. Three independent blinded observers assessed the fusion site (L4-L5 segment) for intersegmental motion by using gentle movements in the coronal and sagittal planes. Any movement at any plane was considered non-fused. When all three observers agreed, the segment was considered completely fused.

Histologic evaluation: After the manual assessment, tissue samples were labeled and kept in a 10% formaldehyde solution (CH2O, MOS®, Moslab, Ankara, Turkey) for approximately 24 hours. Samples were then decalcified, the L3-L6 segments were prepared and the samples were placed in tissue-tracking cassettes. The cassettes were placed in an automatically closed system tissue-tracking device (Shandon®), dehydrated with alcohol and xylene series, and embedded in paraffin (Sasolwax®). Sections with a thickness of 4 micrometers were taken and deparaffinized by drying. Prepared slides were stained with hematoxylin-eosin in an automatic stainer (Sakura®, Tissue-Tek® Otostainer, DRSTM). Slides were evaluated by 2 independent observers using a standard light microscope (Olympus BX-51, Tokyo, Japan). The classification method defined by Emery and Murakami[30]. was used in the histopathological evaluation for assessment of the new bone formation at the L4-L5 level (Figure 6).

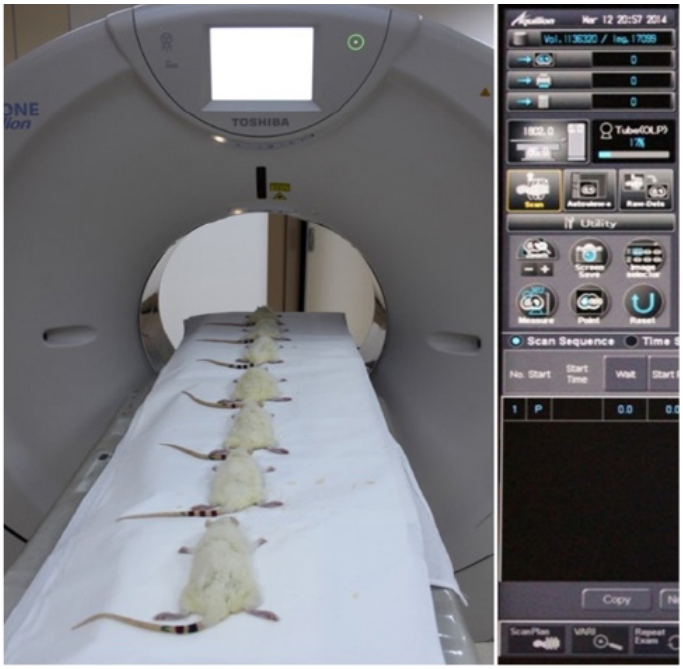

Figure 3. Utilizing a multi-detector computed tomography system to perform computed tomography scans for Sprague-Dawley rats

Statistical Analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological Statistics) programs were used in the analysis of the variables. The conformity of univariate data to normal distribution was evaluated with the Shapiro-Wilk Francia test, while homogeneity of variance was evaluated with the Levene test. While the Mardia (Dornik and Hansen omnibus) test was used for the conformity of multivariate data to the normal distribution, the Box-M test was used for variance homogeneity. The one-way ANOVA (Robust test: Brown-Forsythe) test was used to compare the groups with each other according to quantitative variables, and the Tukey honestly significant difference and Games-Howell tests were used for post hoc analysis. Among the nonparametric tests, the Kruskal-Wallis H test, and Monte Carlo simulation results were used, and Dunn's Test was used for post hoc analysis. The Wilcoxon signed-rank test was tested using Monte Carlo simulation results to compare two replicate measures of quantitative dependent variables. The General Linear Model Repeated-Measures ANOVA test was used to examine the more than two repeated quantitative measurements of its variables and the interaction of these measurements according to the groups, while Fisher's Least Significant Difference was used for the post hoc test. Among non-parametric methods, Friedman's two-way test was tested using the Monte Carlo simulation method, while stepwise step-down comparison tests were used for the post hoc test. In the comparison of the groups according to the categorical variables, the Fisher-Freeman-Halton test was performed with the Monte Carlo simulation technique, and the comparison of the column ratios with each other was expressed with the Benjamini-

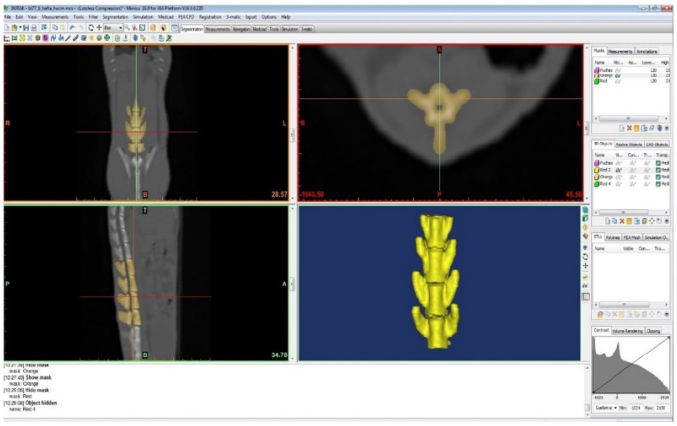

Figure 4. 3D reconstruction view of L3-L6 segment using the Mimics Innovation Suite®

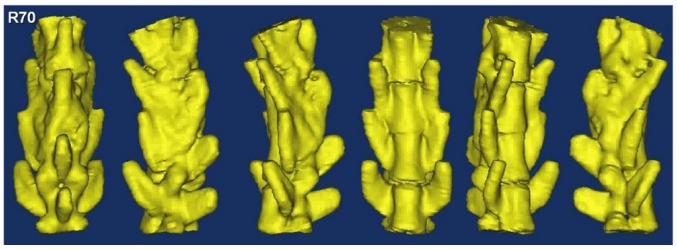

Figure 5. 3D model of a rat from MSC + EPO group in the sixth week. The model is rotated 180° and anterior, posterior, oblique and lateral images were obtained
EPO: Erythropoitein, MSC: Mesenchymal stem cell

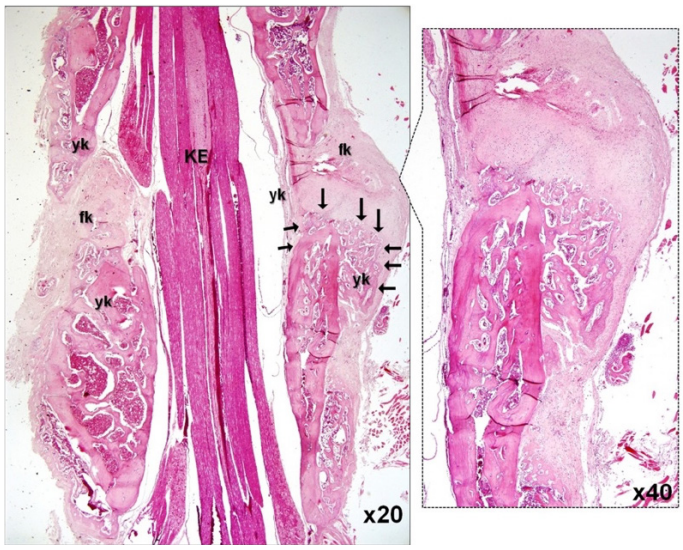

Figure 6. Histopathological specimen which received six points based on the Emery criteria. Note the new bone (yk) formation (black arrows) and a relatively small amount of fibrocartilage (fk) formation
KE: Cauda equina

Hochberg corrected p-value results. Quantitative variables were expressed as mean (standard deviation) and median (minimum/maximum) in the tables, while categorical variables were shown as n (%). The variables were analyzed at a 95% confidence level, and a p-value of less than 0.05 was considered significant.

RESULTS

Direct radiography: EPO + MSC groups had higher fusion rates than those in other groups at the 3rd and 6th weeks. In addition, the fusion rates at weeks 3 and 6 were significantly higher in the EPO + MSC groups than those in the EPO group alone (Table 3a). The highest increase in radiological scores was recorded in the PreS -EPO + MSC groups between the 0th and 3rd months (p=0.018), (Table 3b).

Computed tomography and volumetric measurement: While there was no significant increase in bone volume between 3 and 6 weeks in the EPO group, and between 0 and 3 weeks in the PreS - EPO + MSC groups, a significant increase in bone volume was detected in these intervals in the other fusion models followed for 6 weeks. In addition, the highest bone volume increase in the defined intervals was detected in the PostS - EPO + MSC groups (Table 4).

Manual palpation: The EPO groups had lower fusion rates compared to those in the control and MSC groups (14.3% at both the 3rd and 6th weeks). The PreS - EPO + MSC-3 groups and the PostS - EPO + MSC-6 groups had the highest fusion rates compared to those in the other groups (p=0.048, 71.4%), (Table 5).

Histopathology: The PreS - EPO + MSC-3 groups had the highest histological score among the groups (median=6). The EPO-6 and PostS - EPO + MSC-6 groups had the lowest score for histological examination with a median score of 3, although, there was no statistically significant difference between groups for bone healing (Table 5).

DISCUSSION

The main findings of the study showed that the highest increase in radiological scores was recorded in the PreS - EPO + MSC groups. In addition, the highest bone volume increase in the defined intervals was detected in the PostS - EPO + MSC groups. EPO groups had lower fusion rates compared to those in the control and MSC groups. The PreS - EPO + ESC-3 groups and the PostS - EPO + MSC-6 groups had the highest fusion rates with respect to manual palpation. In addition, the PreS - EPO + ESC-3 groups had the highest histological score among the groups. Briefly, intraperitoneal EPO application delayed the development of cartilage and bone tissue and adversely affected the fusion rates. MSC application alone increased fusion rates compared to the control and EPO groups. In addition, the combined application of MSC and EPO made a significant positive contribution to fusion rates compared to EPO or MSC applications alone. However, there is no significant difference between the applications of EPO at the preoperative 24 hours or the postoperative 72 hours.

EPO and EPO receptors were associated with the enhancement of osteogenic differentiation and mineralization in human and rodent bone marrow osteoblasts, especially in osteoblastic cell cultures with EPO doses between 10 and 100 U/mL[31,32], although, studies showed that EPO promoted *in vitro* osteoclastogenesis at

Table 3a. Radiological evaluation of fusion rates at different measurement points, in groups followed for 6 weeks with comparisons

	Radiography							Pairwise comparison for weeks		
	0. week	3rd week	6th week	Difference (0-3 weeks)	Difference (0-6 weeks)	Difference (3-6 weeks)	p-value			
	Med. (min/max)	Med. (min/max)	Med. (min/max)	Med. (min/max)	Med. (min/max)	Med. (min/max)		(0 vs 3)	(0 vs 6)	(3 vs 6)
2 CT-6	2 (2/2)	2 (1/3)	3 (1/3)	0 (-1/1)	0 (0/1)	1 (-1/1)	0.708[fr]	ns.	ns.	ns.
4 EPO-6	2 (2/2)	1 (1/2)	1 (1/3)	-1 (-1/0)	0 (0/1)	-1 (-1/1)	0.022[fr]	0.048	0.687	0.687
6 MSC-6	2 (2/2)	2 (1/4)	2 (2/3)	0 (-1/2)	0 (-1/1)	0 (0/1)	0.663[fr]	ns.	ns.	ns.
8 PreS - EPO + MSC-6	2 (2/2)	3 (3/3)	2.50 (2/3)	1 (1/1)	-0.50 (-1/0)	0.50 (0/1)	0.007[fr]	0.028	0.582	0.582
10 PostS - EPO + MSC-6	2 (2/2)	3 (3/3)	3 (2/4)	1 (1/1)	0 (-1/1)	1 (0/2)	0.003[fr]	0.023	0.098	0.999
P-value for groups	0.999[k]	0.005[k]	0.158[k]	0.005[k]	0.070[k]	0.158[k]				
2 vs 4	ns.	0.999	ns.	0.999	ns.	ns.				
2 vs 6	ns.	0.999	ns.	0.999	ns.	ns.				
2 vs 8	ns.	0.594	ns.	0.594	ns.	ns.				
2 vs 10	ns.	0.497	ns.	0.497	ns.	ns.				
4 vs 6	ns.	0.677	ns.	0.677	ns.	ns.				
4 vs 8	ns.	0.005	ns.	0.005	ns.	ns.				
4 vs 10	ns.	0.003	ns.	0.003	ns.	ns.				
6 vs 8	ns.	0.999	ns.	0.999	ns.	ns.				
6 vs 10	ns.	0.999	ns.	0.999	ns.	ns.				
8 vs 10	ns.	0.999	ns.	0.999	ns.	ns.				

[fr]Friedman test (Monte Carlo), Post hoc test: Stepwise step-down comparisons, [k]Kruskal Wallis test (Monte Carlo), Post hoc test: Dunn's test.
Med.: Median, min: Minimum, max: Maximum, vs: Versus, ns.: Not significant, MSC: Mesenchymal stem cell, EPO: Erythropoietin, CT: Control

Table 3b: Radiological evaluation of fusion rates at 0th and 3rd weeks in all groups with comparisons

	Radiography			
	0th week	3rd week	Difference (0-3 weeks)	p-value
	Median (min/max)	Median (min/max)	Median (min/max)	(0 vs 3) week
1 CT-3	2 (2/2)	1 (1/2)	-1 (-1/0)	0.061[w]
2 CT-6	2 (2/2)	2 (1/3)	0 (-1/1)	0.999[w]
3 EPO-3	2 (2/2)	1 (1/2)	-1 (-1/0)	0.033[w]
4 EPO-6	2 (2/2)	1 (1/2)	-1 (-1/0)	0.033[w]
5 MSC-3	2 (2/2)	3 (2/4)	1 (0/2)	0.034[w]
6 MSC-6	2 (2/2)	2 (1/4)	0 (-1/2)	0.441[w]
7 PreS - EPO + MSC-3	2 (2/2)	3.1 (3/4)	1.1 (1/2)	0.018[w]
8 PreS - EPO + MSC-6	2 (2/2)	3 (3/3)	1 (1/1)	0.017[w]
9 PostS - EPO + MSC-3	2 (2/2)	3 (2/4)	1 (0/2)	0.033[w]
10 PostS - EPO + MSC-6	2 (2/2)	3 (3/3)	1 (1/1)	0.017[w]
P value for groups	0.999[k]	<0.001	<0.001	
1 vs 7	ns.	0.025	0.025	
2 vs 10	ns.	0.012	0.012	
3 vs 5	ns.	0.011	0.011	
3 vs 6	ns.	0.031	0.031	
3 vs 7	ns.	0.033	0.033	
3 vs 8	ns.	0.012	0.012	
3 vs 10	ns.	0.011	0.011	
4 vs 5	ns.	0.031	0.031	
4 vs 6	ns.	0.033	0.033	
6 vs 10	ns.	0.031	0.031	
7 vs 8	ns.	0.031	0.031	
All other pairwise comparison	ns.	ns.	ns.	

[k]Kruskal Wallis test (Monte Carlo), Post hoc test: Dunn's test, [w]Wilcoxon signed rank test (Monte Carlo).
min: Minimum, max: Maximum, vs: Versus, ns.: Not significant, MSC: Mesenchymal stem cell, EPO: Erythropoietin, CT: Control

Table 4. Final bone volume evaluation at different measurement points with group comparisons

	MDCT; bone volume						p-value	Pairwise comparison for weeks		
				Difference						
	0. week	3rd week	6th week	(0-3 weeks)	(0-6 weeks)	(3-6 weeks)		(0 vs 3)	(0 vs 6)	(3 vs 6)
P (volume*groups)=0.009[g]	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)				
2 CT-6	1281.4 (137.6)	1396.0 (161.8)	1425.8 (158.3)	114.7 (37.5)	144.5 (37.7)	29.8 (22.0)	0.001[g]	<0.001	<0.001	0.012
4 EPO-6	1376.3 (248.8)	1441.8 (267.0)	1477.4 (275.3)	65.5 (34.3)	101.1 (67.7)	35.6 (42.9)	0.015[g]	0.002	0.008	0.071
6 MSC-6	1414.7 (135.8)	1503.8 (122.3)	1551.0 (139.5)	89.1 (40.9)	136.4 (21.0)	47.3 (28.5)	<0.001[g]	0.003	<0.001	0.010
8 PreS - EPO + MSC-6	1560.8 (231.2)	1688.6 (343.0)	1754.7 (348.4)	127.9 (127.1)	193.9 (132.3)	66.0 (24.6)	0.020[g]	0.057	0.016	0.001
10 PostS - EPO + MSC-6	1299.2 (117.9)	1459.9 (107.7)	1551.0 (121.0)	160.7 (56.7)	251.8 (75.9)	91.1 (29.9)	<0.001[g]	<0.001	<0.001	<0.001
P-value for groups	0.086[a]	0.212[a]	0.157[a]	0.187[a]	0.028[a]	0.007[a]				
2 vs 4	ns.	ns.	ns.	ns.	0.597	0.996				
2 vs 6	ns.	ns.	ns.	ns.	0.987	0.843				
2 vs 8	ns.	ns.	ns.	ns.	0.892	0.240				
2 vs 10	ns.	ns.	ns.	ns.	0.052	0.007				
4 vs 6	ns.	ns.	ns.	ns.	0.696	0.959				
4 vs 8	ns.	ns.	ns.	ns.	0.564	0.404				
4 vs 10	ns.	ns.	ns.	ns.	0.015	0.017				
6 vs 8	ns.	ns.	ns.	ns.	0.823	0.826				
6 vs 10	ns.	ns.	ns.	ns.	0.035	0.105				
8 vs 10	ns.	ns.	ns.	ns.	0.871	0.593				

[g]General Linear Model Repeated ANOVA (Wilks' Lambda); Post hoc test: Fisher's least significant difference
[a]One-way ANOVA (Robuts Statistic: Brown-Forsythe), Post hoc test; Games Howell, Tukey HSD
SD: Standard deviation, vs: Versus, ns.: Not significant, MSC: Mesenchymal stem cell, EPO: Erythropoietin, MDCT: Multi-detector computed tomography, CT: Control, HSD: Honestly significant difference

Table 5. Final histopathological score and fusion rate according to manual palpation with group comparisons

	Rat weight (gr)	Histopathology score	Manual palpation	
			Nonunion	Complete fusion
	Mean (SD)	Median (min/max)	n (%)	n (%)
1 CT-3	244.66 (8.34)	5 (2/6)	7 (100)[B]	0 (0)
2 CT-6	240.71 (22.09)	5 (2/6)	4 (57.1)	3 (42.9)
3 EPO-3	247.83 (22.66)	5 (3/5)	6 (85.7)	1 (14.3)
4 EPO-6	245.84 (35.36)	3 (2/6)	6 (85.7)	1 (14.3)
5 MSC-3	254.10 (34.15)	5 (5/6)	3 (42.9)	4 (57.1)
6 MSC-6	253.29 (29.82)	5 (5/6)	4 (57.1)	3 (42.9)
7 PreS - EPO + MSC-3	279.69 (38.01)	6 (5/6)	2 (28.6)	5 (71.4)[A]
8 PreS - EPO + MSC-6	272.64 (42.45)	5 (2/6)	4 (57.1)	3 (42.9)
9 PostS - EPO + MSC-3	274.27 (29.32)	5 (2/6)	6 (85.7)	1 (14.3)
10 PostS - EPO + MSC-6	232.23 (17.75)	3 (2/6)	2 (28.6)	5 (71.4)[A]
p-value	0.062[a]	0.149[k]	0.038[f]	

[a]One-way ANOVA (Robuts Statistic: Brown-Forsythe), [k]Kruskal Wallis test(Monte Carlo), [f]Fisher Freeman Halton (Monte Carlo), Post hoc test: Benjamini-Hochberg correction
[A]Significant according to nonunion (manual palpation), [B]Significant according to complete fusion (manual palpation)
SD: Standard deviation, min: Minimum, max: Maximum, MSC: Mesenchymal stem cell, EPO: Erythropoietin, CT: Control

doses ranging from 5 to 20 U/mL or lower concentrations[23,31,32]. Recent reviews concluded that the EPO mechanisms producing beneficial effects on bone volume were unknown, and pointed to the different cell types with different responses to EPO during bone remodeling and repair, and concentrations of EPO[22,23]. Rölfing et al.[21] showed a significant increase in bone volume with subcutaneous injections of EPO compared to that in the control group in a rabbit posterolateral spinal fusion model. They also reported higher but not significant fusion rates in the EPO group, examined with MDCT, manual palpation, and X-ray, so they supported EPO as an autograft-enhancing factor[21]. Later, the same team reported that topical use of EPO with a collagen carrier significantly increased the median bone volume fraction by 1.06 compared to that in the control group in an animal study with adolescent pig's calvarial bone[33]. Omlor et al.[34] reported significantly increased bone formation and vascularization with local and systemic administration of EPO according to histomorphometric and radiological evaluation. In addition, they concluded that a direct local application of EPO (single dose) during surgery was sufficient to increase bone healing substantially[34]. Contrary to the majority of the current literature, in our study EPO has no additional benefit for bone volume compared to other groups, and had histologically lower fusion rates, although these were not significant. This supports both the osteogenic and osteolytic effects of EPO, which have been noted in systematic reviews previously.

Preclinical and clinical studies demonstrated that MSC improved successful spinal fusion with osteogenic and osteoinductive properties. The differing designs of existing studies, heterogeneous groups, the use of different animal models, various scaffolds, a combination of various growth factors, donor sites, and the harvesting and culturing mediums of MSC preclude the formation of a consensus for the development of a standard technique for MSC use[1,2]. Nakajima et al.[15] showed higher fusion rates in rabbit spines treated with MSC plus autograft compared to those in the control group. Minamide et al.[35] also reported increased fusion rates in the control group in rabbit models with bone marrow-derived MSC culture-supported growth factors, when compared with autograft. Additionally, adipose-derived MSC is beneficial with respect to fusion rates in both a rat and rabbit model of posterolateral fusion[11,36]. Current reviews indicate higher fusion rates of up to 100% with MSC application isolated from bone marrow harvested from the iliac crest or vertebral body intraoperatively and then transplanted[1,37]. However, due to the heterogeneity of the studies, valid comparisons cannot be made. Currently, randomized controlled studies are continuing with respect to MSC use and spinal fusion. In the present study, MSC administration achieved higher fusion rates and the combination of EPO + MSC application showed additionally significant benefits according to radiological and histological examination. The differentiation potential of MSC into osteoblasts may have been stimulated by EPO, and the results of this study support this hypothesis. The increased impact of MSC with BMP and the basic fibroblast growth factor has been demonstrated in an animal study. The stimulation of spinal fusion with various growth factors also continues to be explored and debated[38]. In spinal fusion, the current literature would indicate that it is possible to increase the success rate by combining different carrier elements with different biological agents. However, the presence of other factors, such as cost and patient selection, as well as treatment selection, will continue to be compelling factors for the establishment of standard approaches.

Study Limitations

The interaction of EPO with MSC treatment resulted in positive results at the macro evaluation, but the lack of an examination method such as flow cytometry and comparison with different growth factors are major limitations of the study.

CONCLUSION

MSC administration achieved a higher fusion rate and the combination of an EPO + MSC application showed further significant benefits according to radiological and histological examination. However, EPO confers no additional benefit for bone volume compared to other groups. The curative efficacy of MSC or EPO + MSC treatments in spinal fusion is confirmed by the literature and this study. However, the application of EPO alone has two-sided (benefit/harm) effects. On the other hand, the stimulation/direction of MSC with a growth factor such as EPO or the widely accepted BMP seems to be meaningful and more effective.

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Ethics

Ethics Committee Approval: This study was approved by Gülhane Military Medical Academy Animal Experiments Ethical Committee (decision no: 13/128, date no: 22.11.2013).
Informed consent: Experimental animal study.
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Authorship Contributions

Surgical and Medical Practices: A.B.B., Ç.N., Concept: A.B.B., Design: A.B.B., E.O., Data Collection or Processing: A.B.B., Ç.N., Y.E., Analysis or Interpretation: A.B.B., Y.E., Literature Search: A.B.B., Writing: A.B.B., Ö.E., E.O.
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