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RADIOISOTOPIC EVALUATION OF REPARATIVE OSTEOGENESIS IN VARIOUS FORMS OF OSTEOMYELITIS OF THE MANDIBLE

M.P. Komskyi [1], Ye.G Romanenko [2]*, I.G. Lisova [3], G.I. Titov [1], O.S. Trushenko [1], Ya.V. Lavreniuk [2]

Dniprovskyi Medical Institute of Traditional and Non-Traditional Medicine [1]
Sevastopolska str., 17, Dnipro, 49027, Ukraine
Dnipro State Medical University [2]
Volodymyra Vernadskoho str., 9, Dnipro, 49044, Ukraine
Kharkiv Medical Academy of Postgraduate Education [3]
Amosova str., 58, Kharkiv, 61175, Ukraine
Дніпровський медичний інститут традиційної і нетрадиційної медицини [1]
вул. Севастопольська, 17, Дніпро, 49027, Україна
Дніпровський державний медичний університет [2]
вул. Володимира Вернадського, 9, Дніпро, 49044, Україна
Харківська медична академія післядипломної освіти [3]
вул. Амосова, 58, Харків, 61175, Україна
**e-mail: helenromanenko2017@gmail.com*

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Ключові слова: *остеомієліт, перелом нижньої щелепи, сцинтиграфія, діагностика, репаративний остеогенез, ремоделювання кістки*

Abstract. Radioisotopic evaluation of reparative osteogenesis in various forms of osteomyelitis of the mandible. Komskyi M.P., Romanenko Ye.G., Lisova I.G., Titov G.I., Trushenko O. S., Lavreniuk Ya.V. *The aim of this work is the rationale for using radiological method of examination in diagnosing and monitoring the mandibular osteomyelitis treatment. A total of 60 patients with traumatic (first group) and odontogenic (second group) mandibular osteomyelitis were examined. Among them, there were 24 (40%) males and 36 (60%) females aged between 20 and 45 years. The patients received intravenous injection of Technefor (^{99M}Tc) with the radiation activity of 300-400 megabecquerel 3-4 hours before scintigraphy. The mandible radiopharmaceutical uptake was measured using a computerized gamma camera. The level of ^{99M}Tc accumulation in the bone tissue was quantified by gamma-radiation. A patient was examined on the day of hospital admission and on day 14 after surgical treatment of osteomyelitis of the mandible. Our studies have shown that all forms of traumatic and odontogenic osteomyelitis are accompanied by significant changes in ^{99M}Tc uptake in the mandible, however, both ^{99M}Tc uptake and its decrease after surgical treatment were most obvious in odontogenic osteomyelitis. The increase in ^{99M}Tc uptake in traumatic mandibular osteomyelitis was 38,1% (up to 1669,9 gamma-radiation pulses), 140,9% (up to 2913,7 gamma-radiation pulses) and 129% (up to 2772,7 gamma-radiation pulses) in the acute, subacute and chronic stages of the disease, respectively. The increase in ^{99M}Tc uptake in odontogenic mandibular osteomyelitis was 160,0% (up to 3144,1 gamma-radiation pulses), 218,1% (up to 3846,6 gamma-radiation pulses) and 275,2% (up to 4537,6 gamma-radiation pulses) in the acute, subacute and chronic stages of the disease, respectively. The increase in ^{99M}Tc uptake was due to blood flow enhancement, metabolic disorders, activation of osteoblast and osteoclasts in the bone tissue. The decrease in ^{99M}Tc uptake after the treatment indicated the positive response to treatment. Scintigraphic examination was more sensitive and specific in comparison to X-ray diagnostics of mandibular ostemyelitis. The sensitivity of scintigraphic findings ranged from 60.0% to 100%, and the specificity was 100% at different stages of ostemyelitis.*

Реферат. Радіоізотопна оцінка стану репаративного остеогенезу при різних формах остеомієліту нижньої щелепи. Комський М.П., Романенко О.Г, Лісова І.Г., Тітов Г.І., Трушенко О.С., Лавренюк Я.В. *Метою цієї роботи є обґрунтування використання радіологічної методики обстеження для діагностики та контролю лікування остеомієліту нижньої щелепи. Було обстежено 60 пацієнтів з травматичним (1 група) та одонтогенним (2 група) остеомієлітом нижньої щелепи. З них 24 (40%) чоловіки й 36 (60%) жінок у віці від 20 до 45 років. Пацієнтам вводили препарат Технефор (^{99M}Tc), активністю 300-400 мегабекерелей внутрішньовенно за 3-4 години до проведення сцинтиграфії. Вимірювання акумуляції радіологічного фармакологічного препарату в нижній щелепі проводили з використанням комп'ютеризованої гамма-камери. Рівень накопичення ^{99M}Tc у кістковій тканині оцінювали в кількості імпульсів γ – випромінювання. Дослідження проводили при надходженні до стаціонару й на 14 добу після оперативного лікування. Наші дослідження показали, що зміни акумуляції ^{99M}Tc у нижній щелепі достовірно відбуваються при всіх стадіях травматичного й одонтогенного остеомієліту, проте як накопичення ^{99M}Tc, так і зниження його рівня після оперативного лікування найбільш помітні при одонтогенному остеомієліті. При травматичному остеомієліті нижньої щелепи підвищення рівня накопичення ^{99M}Tc на 38,1% (до 1669,9 імпульсів γ- випромінювання), 140,9% (до 2913,7 імпульсів γ-випромінювання), 129% (до 2772,7 імпульсів γ- випромінювання) характерно для гострої, підгострої і хронічної стадій захворювання відповідно. При одонтогенному остеомієліті нижньої щелепи підвищення рівня накопичення 99MTc на 160,0% (до 3144,1 імпульсів γ-випромінювання), 218,1% (до 3846,6 імпульсів γ-випромінювання), 275,2% (до 4537,6 імпульсів γ-випромінювання)) характерно для гострої, підгострої і хронічної стадій захворювання відповідно. Підвищення рівня накопичення ^{99M}Tc пов'язано з посиленням кровотоку, порушенням метаболізму, активацією остеобластів й остеокластів у кістковій тканині. Зниження рівня накопичення ^{99M}Tc після лікування свідчить про позитивну динаміку перебігу запального процесу. Сцинтиграфічне дослідження було більш чутливим і специфічним методом порівняно з рентгенологічною діагностикою остеомієлітів нижньої щелепи. Чутливість сцинтиграфічного дослідження становила від 60,0% до 100%, а специфічність – 100% при різних стадіях остеомієліту.*

Inflammatory processes underlying pathogenesis of various acute and chronic diseases are characterized by medical and social significance as being associated with high rates of septic complications and potentially fatal outcomes[19]. Osteomyelitis of the jaws is an infectious suppurative-necrotizing process that develops in the bone and surrounding soft tissues. Jaw osteomyelitis is predominantly odontogenic (dental infection related), traumatic (fracture related), hematogenous and specific in nature. The most common origin of osteomyelitis is odontogenic and traumatic. The early diagnostics of osteomyelitis is crucial considering that inadequate or delayed diagnosis significantly undermines a possibility of cure and increases a grade of disease complications [7, 8, 13, 18].

Bone scintigraphy presents high sensitivity, especially in patients with suspected or established inflammatory disease or malignant tumor [2]. Since functional disorders in the bone occur earlier than structural, radionuclide bone scanning demonstrates inflammatory process activity and lesion sizes [3, 17].

However, the current literature insufficiently covers the quantitative scintigraphic characteristics to diagnose different forms and stages of jaw osteomyelitis as well as to measure its treatment outcomes [4, 8].

Analyzing isolated cases of mandibular osteomyelitis therapy has led to the conclusion that scintigraphy can be useful for assessing the bone inflammatory activity and response to treatment in patients with osteomyelitis of the mandible [8, 16]. More examinations with a larger number of patients are needed to identify the indicators characterizing the treatment dynamics in the bone lesions [10, 11, 17].

The aim of this work is the rationale for using radiological method of examination in diagnosing and monitoring the mandibular osteomyelitis treatment.

MATERIALS AND METHODS OF RESEARCH

A total of 60 patients who visited the Maxillofacial Department of City Clinical Hospital No. 4 were examined from 2015 to 2019 in the furtherance of this goal. Among them, there were 24 (40%) males and 36 (60 %) females aged between 20 and 45 years. The first group included 30 patients with traumatic mandibular osteomyelitis. The second group consisted of 30 patients with odontogenic osteomyelitis. Three stages of osteomyelitis were distinguished by the disease duration: acute, subacute, and chronic.

The patients were assigned to the groups following the study objective based on inclusion/exclusion criteria:

Inclusion criteria were: patients of both sexes who presented with clinically and radiologically proven osteomyelitis managed conservatively or surgically.

Patients with a past history of the head and neck radiotherapy were excluded.

The study design was reviewed and approved by the Ethics Committee of Dnipro State Medical University (Project number 097-15). Medical information about the patients was fully anonymous; none of them participated in any experimental trials. Prior to the examination, the patients signed a written informed consent.

The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – “Ethical principles for medical research involving human subjects” and “Universal Declaration on Bioethics and Human Rights” (UNESCO).

Study methodology. Patients with odontogenic and traumatic mandibular osteomyelitis received intravenous injection of Technefor (^{99M}Tc) with the radiation activity of 300-400 megabecquerel 3-4 hours before scintigraphy [7].

A mandible radiopharmaceutical uptake was measured simultaneously in both hemi-mandibles in the supine position of patients using a computerized gamma camera GKS-200k. The hemi-mandible without pathological process was used for control measurements. The level of ^{99M}Tc accumulation in the bone tissue was quantified by gamma-radiation. A patient was examined on the day of hospital admission and on day 14 after surgical treatment of osteomyelitis of the mandible. Initial intensity of ^{99M}Tc uptake in the healthy hemi-mandible of the patients was 1209.3±46.1 and on follow-up day 14 – 1197.7±23.0 gamma-radiation pulses, respectively.

Statistical analysis. Statistical analysis was performed with the software package Statistica 6.1 for Windows (serial number AGAR 909 E415822FA) [15]. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of plain radiography and scintigraphic imaging in mandibular ostemyelitis were calculated.

RESULTS AND DISCUSSION

The results of ^{99M}Tc uptake in persons with mandibular osteomyelitis are presented in Table 1.

The studies have shown significant variations in ^{99M}Tc uptake in the mandible tissues in different stages of osteomyelitis. This process involves metabolic changes in the maxillofacilal bones and surrounding structures. Metabolically active areas appear as increased uptake of an indicator and are known as “hot spots”. “Cold spots” are the areas of insufficient or decreased uptake of indicators demonstrating impaired osteogenesis or blood supply to the scanned area.

The level of ^{99M}Tc uptake in acute and subacute stages of TMO significantly exceeded that estimated in the healthy hemi-mandible ($p_{control}$<0.01). The indicators changed significantly in acute stage of the disease transition to subacute one. It could be an important signal for the timely change of treatment tactics. In the subacute stage of the disease, the zone of infectious inflammatory process in the jaw and adjacent soft tissues was localized. The lesion zone was lined by granulation tissue. Increasing ^{99}MTc uptake indicated both granulation and bone tissue metabolic activity. In the chronic stage of TMO, periosteal osteogenesis was attenuated, and there was a completion of bone sequestrum and involucrum formation.

After 14-day course of treatment, including surgery and standard postoperative therapy, no significant changes in ^{99M}Tc uptake were observed in patients with acute and subacute TMO, while there was only a downward trend in subacute stage. In chronic TMO, the results of scintigraphy also indicated an increase in the initial index of gamma-radiation pulses number by 129.2% compared with the control index (Fig.).

The level of ^{99M}Tc uptake increased significantly compared with acute TMO by 66.0%, but not with subacute stage. After 14 days of inpatient treatment for chronic TMO, ^{99M}Tc uptake decreased by 28.9%

when compared with the admission indicator. This reflected a decrease in the inflammatory process activity and soft tissue hyperemia after the therapy. Slightly different changes in the level of radio-pharmaceutical drug in the mandibular tissues were observed in odontogenic mandibular osteomyelitis (OMO).An increase in the admission indicator was 160.0% (p <0.01) in acute OMO, 218.1% (p <0.01) – in subacute, and 275.2% (p <0.01) – in chronic as compared with the control indicators.

Table 1

Mandibular scintigraphic uptake of ^{99M}Tc (number of gamma-radiation pulses) in patients of the examined groups

Series of observations	Statistical indicators	Stages of the disease			
Traumatic mandibular osteomyelitis (n=30)					
	M±m	Control (n=30)	Acute (n=9)	Subacute (n=10)	Chronic (n=11)
Baseline indicators	M	1209,3	1669.9 $p_{control}<0.05$	2913.7 $p_{control}<0.01$	2772.1 $p_{control}$, $p_1<0.01$ $p_1<0.01$
	±m	46,1	103.7	426.1	140.5
Day 14 after surgery	M	1197,7	1589.3 $p_{control}<0.05$	2130.0 $p<0.05$ $p_{control}<0.01$ $p_{control}<0.01$	1969.4 $p, p_{control}<0.01$ $p_1<0.05$
	±m	23,0	80.6	552.8	47.2
Odontogenic mandibular osteomyelitis (n=30)					
	M±m	Control (n=30)	Acute (n=8)	Subacute (n=12)	Chronic (n=10)
Baseline indicators	M	1201,4	3144.1 $p_{control}<0.01$	3846.6 $p_{control}<0.01$	4537.6 $p_{control}$, $p_1<0.01$ $p_2<0.05$
	±m	32,1	195.8	218. 8	184.3
Day 14 after surgery	M	1191,8	1692.9 $p<0.01$ $p_{control}<0.05$	2280.3 $p, p_{control}<0.01$	2879.2 $p, p_{control}<0.01$ $p_1<0.05$
	±m	26,4	264.9	310.9	312.9

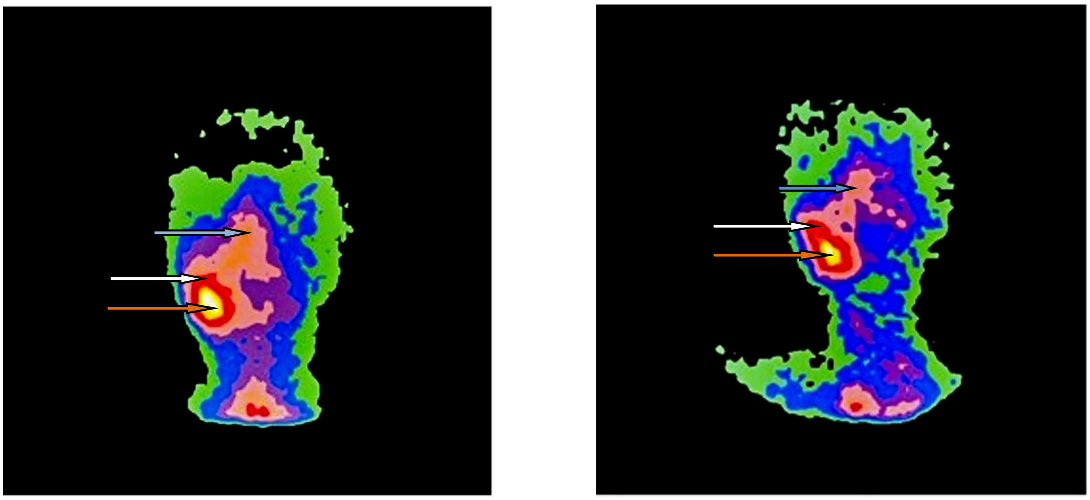
Notes: p – compared with the baseline indicators; $p_{control}$ -compared with the control group; p_1- compared with acute stage; p_2 -compared with subacute stage of osteomyelitis.

Moreover, ^{99M}Tc uptake in chronic OMO was significantly higher than that in acute (by 44.3%) and subacute (by 14.2%) stages. Following the conventional inpatient treatment, the level of ^{99M}Tc uptake in acute OMO was 41.3% higher than the control indicator and 2 – 2.5 times higher than that in subacute and chronic stages. In patients with chronic OMO as in chronic TMO, the level of ^{99M}Tc uptake showed a decline of 36.5% (p<0.01) 14 days after the surgery compared with the admission level.

The sensitivity of the examination was 60% in the subacute stage of ostemyelitis, 91% – in the chronic, 100% – in the acute stage of ostemyelitis, the specificity was 100% in all stages of TMO (Table 2).

In odontogenic ostemyelitis, the sensitivity of scintigraphy was 72.7% in the subacute stage of ostemyelitis, 91% – in the chronic, 100% – in the acute stage, the specificity – 100% in all stages of ostemyelitis.

The method was highly sensitive and specific (>91%), though the sensitivity was 60 and 72.7% in TMO and OMO, respectively, in the subacute stage of mandibular ostemyelitis (a total of 7 FN results were recorded). It was related to the ^{99}MTc accumulation in the area of well-vascularized granulation tissue, which impeded the differential diagnosis between different stages of ostemyelitis.



a b

Scintigraphy of a 28-year-old patient E. Diagnosis: Chronic stage of traumatic mandibular osteomyelitis; a - before surgery (^{99M}Tc uptake - 370%); b - postoperative day 14 (^{99M}Tc uptake - 210%). Increased radiotracer uptake in the area of reparative periosteal ossification (a; white arrow) and completion of an involucrum formation including a pyogenic capsule and a bone sequestrum (a; yellow arrow) confirm the diagnosis of chronic mandibular osteomyelitis. Diffuse radiotracer uptake in the soft tissues of the right temporomandibular region also demonstrates inflammation and increased blood flow (a;blue arrow). The radiotracer accumulation in the area of reparative periosteal osteogenesis (b; white arrow) and a decrease in the sequestrum size (b; yellow arrow) indicate a decrease in the intraosseous inflammatory process activity. Accordingly, the area of soft tissue hyperemia in the right temporomandibular region is reduced (b; blue arrow)

Radionuclide imaging had the highest PPV of 100% and NPV of >83.3% in all stages of TMO and OMO. We have found that scintigraphic findings were sensitive and specific in diagnosis of mandibular ostemyelitis.

A number of instrumental methods of examination are used to diagnose maxillofacilal injuries. X-ray examination is important in diagnosing chronic jaw osteomyelitis. Since density confluence of cortical and cancellous bone, cortices (particularly in the mandible) have a masking effect on lesions within the cancellous bone, which is predominantly affected in osteomyelitis, destruction may not appear. Meaningful radiographic features are usually absent in subacute stage of osteomyelitis. Only with rapid progression of the disease, the cortical bone destruction is manifested radiologically. The diagnostic accuracy of X-ray for early detection of osteomyelitis is 50-60% [5, 7].

Given the shortcomings of X-ray, modern diagnostic methods such as computer tomography (CT) and magnetic resonance imaging (MRI), scintigraphy, infrared thermography, fistulography are applied [11, 12, 14, 15]. Rheography and Doppler sonography are used for assessing regional blood flow; ultrasonography serves for monitoring the bone tissue healing in pathological lesions allowing to trace the dynamics of its state in a treatment course with less radiation exposure.

CT is useful in the pre-surgical treatment planning of acute traumatic osteomyelitis and diagnosing the acute phase of the disease evolution to chronic. Changes in the bone tissue may not be obvious until 10 to 14 days from the disease onset on CT, as well as on X-ray. Contrast-enhanced CT helps in visualizing the soft tissues involvement [6, 9].

The use of laser Doppler flowmetry to diagnose osteomyelitis is mentioned by some authors. Studies have shown that medullary bone inflammation leads to a decrease in mandibular blood flow [5, 13]. Gadolinium-enhanced MRI has detected early changes in acute osteomyelitis [16]. MRI is considered non-specific to ensure accurate diagnosis, but may be useful for dynamic patient follow-up [4].

Among the most sensitive diagnostic methods is radiological examination of patients. Radioactive isotopes of technetium (^{99M}Tc) with cumulative uptake both in bone and soft tissues of the whole body are commonly used in diagnosing bone lesions. Progress in technetium chemistry over the past 15 years has enhanced to the development of new radiopharmaceuticals with significantly improved clinical potential. Oncology, cardiology, neurology and infection/inflammation imaging are identified as areas in which ^{99M}Tc radiopharmaceuticals could make substantial contributions in the future [18]. An increased ^{99M}Tc accumulation was observed both in areas of high osteoblastic activity and hyperemia. Some authors believe that this fact can induce false positive scintigraphic results in the weeks or months following recovery or successful surgery and is a sign of local bone remodeling [7]. The sensitivity of ^{99M}Tc scintigraphy in the diagnosis of osteomyelitis is 80-100% [1]. Patients who have signs suggestive of increased radiopharmaceutical uptake on early scintigraphic images do not need to be re-examined later to clarify a diagnosis. It is bone scintigraphy that helps to diagnose chronic osteomyelitis, often two weeks before changes become apparent on conventional radiological images (X-ray, CT), allowing timely surgery on a patient to remove a sequestration of the mandibular bone. According to some authors, radionuclide imaging should be used for the diagnosis of acute osteomyelitis only. At the early stages of the disease, bone scintigraphy enables precise localization of an inflammatory focus in the bone tissue. Sites of bone lesions are visually represented by hypervascular areas on ^{99M}Tc scintigraphic images. However, it is difficult to differentiate osteomyelitis from other soft tissue purulent diseases which may occur with the similar manifestations. Our studies have shown that all stages of traumatic and odontogenic osteomyelitis are accompanied by significant changes in ^{99M}Tc uptake in the mandible, however, both ^{99M}Tc uptake and its decrease after surgical treatment were most obvious in odontogenic osteomyelitis. This fact demonstrates the blood flow restoration and normalization of bone metabolism in the area of postoperative wound healing.

Table 2

Statistical characteristics of scintigraphic imaging in patients with TMO and OMO (n=60)

Stage of the disease	TN	TP	FN	FP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Acc (%)
Traumatic mandibular osteomyelitis (n=30)									
n/N (%)									
Acute (n=9)	21/30 70.0	9/30 30.0	0	0	100	100	100	100	100
Subacute (n=10)	20/30 66.7	6/30 20.0	4/30 13.3	0	60.0	100	100	83.3	86.7
Chronic (n=11)	19/30 63.4	10/30 33.3	1/30 3.3	0	90.9	100	100	95.0	96.7
Odontogenic mandibular osteomyelitis (n=30)									
Acute (n=8)	22/30 73.3	8/30 26.7	0	0	100	100	100	100	100
Subacute (n=12)	18/30 60.0	9/30 30.0	3/30 10.0	0	72.7	100	100	85.7	90.0
Chronic (n=10)	20/30 66.7	9/30 30.0	1/30 3.3	0	90.9	100	100	95	96.7

Notes: TN – true-negative, TP – true-positive, FN - false-negative, FP - false-positive, PPV - positive predictive value, NPV - negative predictive value, Acc – accuracy.

CONCLUSIONS

1. The study has provided the main scintigraphic findings on bone-seeking agent uptake depending on the form of osteomyelitis. The proposed quantitative criteria have enabled an objective assessment of bone tissue remodeling rate, therapeutic decision and predicting the probability of the disease recurrence in different forms of osteomyelitis.
2. The increase in ^{99M}Tc uptake in traumatic mandibular osteomyelitis was 38.1% (up to 1669.9 gamma-radiation pulses), 140.9% (up to 2913.7 gamma-radiation pulses) and 129% (up to 2772,7 gamma-radiation pulses) in the acute, subacute and chronic stages of the disease, respectively.
3. The increase in ^{99M}Tc uptake in odontogenic mandibular osteomyelitis was 160.0% (up to 3144.1 gamma-radiation pulses), 218.1% (up to 3846.6 gamma-radiation pulses) and 275.2% (up to 4537.6 gamma-radiation pulses) in the acute, subacute and chronic stages of the disease, respectively. The increase in 99MTc uptake was

due to blood flow enhancement, metabolic disorders, activation of osteoblast and osteoclasts in the bone tissue. The decrease in ^{99M}Tc uptake after the treatment indicated the positive response to treatment.

4. Scintigraphic examination was sensitive and specific in diagnostics of mandibular ostemyelitis. The sensitivity of scintigraphic findings ranged from 60.0% to 100%, and the specificity was 100% at different stages of ostemyelitis.

Contributors:

Komskyi M.P. – data collection, methodology;

Romanenko Ye.G. – conceptualization, data analysis;

Lisova I.G., Titov G.I. – design;

Trushenko O.S., Lavreniuk Ya.V. – methodology.

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