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C-TERMINAL TELOPEPTIDE LEVEL IN "KROKODIL" DRUG-RELATED JAW OSTEONECROSIS PATIENTS

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Abstract

"Krokodil" is a synthetic drug, for synthesis of which red phosphorus is used. The mixture is used intravenously. Drug abusers use "Krokodil" without clearing and many side products enter the bloodstream. Among these side products phosphorus-containing substances are present. In such patients jaw osteonecrosis develops. Dental extraction is main predicting factor of osteonecrosis development. Jaw bone exposure (up to 92.2%) is main clinical presentation of this disease.

C-terminal telopeptide is biochemical marker to measure bone remodeling and bone resorption. In patients with increased bone turnover elevated C-terminal telopeptide value is found. C-terminal telopeptide decreased level is found in patients with jaw osteonecrosis taking anti-resorptive medication. There is a relationship between low serum C-terminal telopeptide values and increased incidence of jaw osteonecrosis.

Retrospective study of 17 "Krokodil" drug-related jaw osteonecrosis patients was performed. They were all male patients with a mean age of 40.65±2.10 (range 25-56) years. All patients had used "Krokodil" in the past (mean 27.4±3.9 months, range 5-72 months) and all of them had stopped its use a minimum of 1 month before surgery. Drug withdrawal period was 5.1±1 months (range 1-15 months). Patients were divided into two groups: I group (9 patients) – patients without any signs of demarcation or sequestrum formation, II group (8 patients) – patients with osteonecrosis zone demarcation or sequestrum formation. In I group decreased level of serum C-terminal telopeptide was found. This shows the decreased bone turnover, which is the result of "Krokodil" use. Thus, "Krokodil" drug has anti-resorptive effect on bone tissue. This means that jaw osteonecrosis in "Krokodil" abusers is a new type of medication-related osteonecrosis of the jaw. In II group mean level of C-terminal telopeptide was significantly higher than in I group. There was a very strong, positive correlation between C-terminal telopeptide mean level and the presence of demarcation or sequestrum formation, which was statistically significant. High level of serum C-terminal telopeptide indicates the improved bone turnover. This makes possible the osteonecrosis zone demarcation and sequestrum formation.

Keywords: *"Krokodil" drug, jaw osteonecroosis, C-terminal telopeptide, jaw resection.*

Introduction

"Krokodil" is the street name of the mixture of a new synthetic drug. Desomorphine is an active substance of "Krokodil", which is an opiate. It is widely used over the territory of former USSR (Russia, Ukraine, Armenia and others). There are reports of "Krokodil" use from Europe and USA [*Lemon T, 2013*; *Haskin A et al., 2016*]. Drug abusers synthesize "Krokodil" themselves. They use cheap and commonly available substances, which are easily obtained in the drug-stores or various shops. Codeine containing analgesics ("Sedalgin", "Pentalgin" etc), iodine, soda, red phosphorus (from match boxes), hydrochloric acid, gasoline and similar substances are used for this purpose.

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The mixture is used intravenously. Drug abusers use "Krokodil" without clearing, and many side products enter the bloodstream. Among these side products phosphorus-containing substances are present [*Alves E et al., 2015*]. Jaw osteonecrosis occurs as a common complication in "Krokodil" users. Dental extraction is main predicting factor of osteonecrosis development [*Hakobyan K, 2013*]. Jaw bone exposure (up to 92.2%) is main clinical presentation of this disease (Fig. 1) [*Malanchuk V et al., 2007; Tymofieiev A, Dakal A, 2010; Medvedev Yu, Basin E, 2012; Hakobyan K, 2013*].

Surgery is the main method of treatment for "Krokodil" drug-related jaw osteonecrosis patients. Main factors of treatment success are: 1) withdrawal of "Krokodil" use in pre- and postoperative periods, 2) resection of necrotic tissues for a minimum in 0.5 *cm* beyond the visible borders of osteonecrosis. Leading to this treatment option no cases of reoccurrence were reported in maxilla. In the mandible recurrence rate was 23% [*Poghosyan Yu et al., 2014*].

Radiographic methods are less informative for diagnosis of "Krokodil drug-related jaw osteonecrosis patients. Nonspecific signs (osteosclerosis, destruction, empty dental sockets without demarcation of osteonecrotic zone) are often revealed in early periods of the disease. In some cases demarcation found in CT-scan was not clinically determined during surgeries [*Poghosyan Yu et al., 2013*].

Mechanism of "Krokodil" drug-related jaw osteonecrosis is unknown. Poisoning by phosphorus compounds is seen in patients using home-made narcotics for the synthesis of which red phosphorus is used [*Tymofieiev A, Lesova I, 2009*]. Also, there are no data, that other components of the mixture can cause jaw osteonecrosis. This allows thinking that new type of phosphoric necrosis of the jaw is developed in "Krokodil" abusers [*Medvedev Yu, Basin E, 2012*]. Due to antiresorptive nature of phosphoric necrosis of the jaw there is decreased level of serum C-terminal telopeptide in patients with this disease [*Marx R et al., 2007*].

Type 1 collagen is the main component of organic-bone matrix. During normal bone metabolism, type 1 collagen is degraded, and fragments pass into bloodstream. Serum carboxyterminal cross-linking telopeptide (C-terminal telopeptide) is one of such fragments. C-terminal telopeptide is biochemical marker to measure bone remodeling and bone resorption [*Rosen H et al., 2000*]. In patients with increased bone turnover elevated C-terminal telopeptide value is found. Decreased level of C-terminal telopeptide is found in patients with jaw osteonecrosis (patients with medication-related osteonecrosis of the jaw) taking anti-resorptive medication (e.g. Bisphosphonates) [*Marx R et al., 2007*]. According to R. Marx and co-authors (2007) there is a relationship between low serum C-terminal telopeptide values and increased incidence of jaw osteonecrosis. The authors reported that a value of less than 100 *pg/ml* represented a high risk of medication-related osteonecrosis of the jaw; 100 to 150 *pg/ml*, a moderate risk; greater than 150 *pg/ml*, minimal or no risk. In patients with C-terminal telopeptide level more

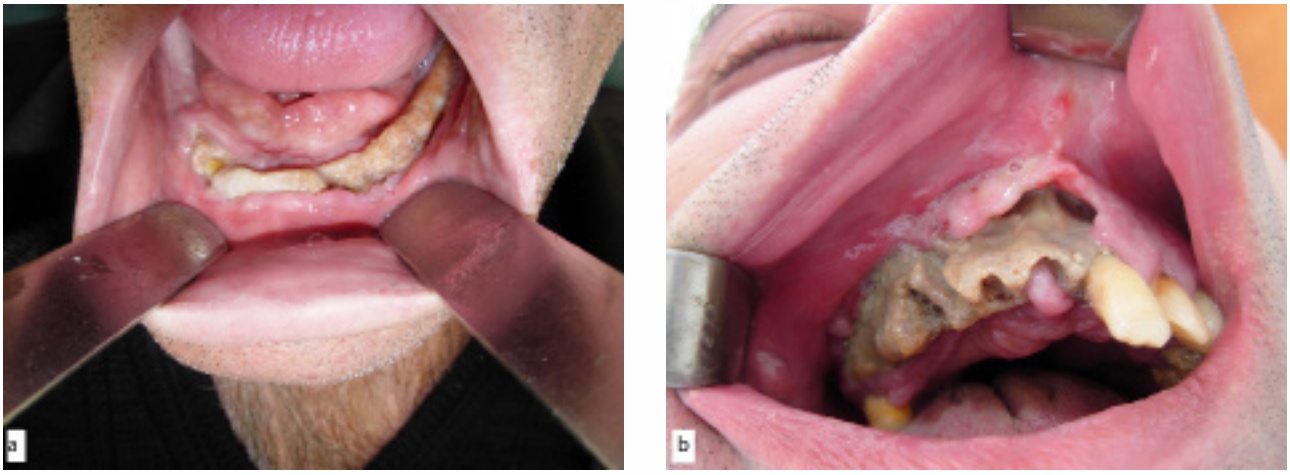

Figure 1. *Oral cavity view of "Krokodil" drug-related jaw osteonecrosis patients: (a) exposure of mandible, (b) exposure of maxilla*

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than 150 *pg/ml* osteoclast function returns to reasonable levels and bone healing is more predictable [*Marx R, 2009*]. There are controversial statements about C-terminal telopeptide use as predictive factor for jaw osteonecrosis development after oral surgery procedures. According to Marx R and co-authors (2007), its values were noted to increase between 25.9 *pg/ml* to 26.4 *pg/ml* for each month of a bisphosphonate holiday. This indicates the recovery of bone remodeling and a guideline as to when oral surgical procedures can be accomplished with the least risk [*Marx R et al., 2007*]. Controversially, J. O'Connell and co-authors (2012) showed that the C-terminal telopeptide test is not predictive for the development of medication-related osteonecrosis of the jaw following oral surgery. The C-terminal telopeptide test should not be used in isolation to withhold or initiate treatment in patients exposed to bisphosphonates [*O'Connell J et al., 2012*].

The aim of this study was to determine C-terminal telopeptide level in "Krokodil" drug-related jaw osteonecrosis patients to approve antiresorptive nature of "Krokodil" drug-related jaw osteonecrosis. Also, correlation between C-terminal telopeptide level and presence of necrotic bone demarcation is determined.

Material and methods

Retrospective study of 17 "Krokodil" drug-related jaw osteonecrosis patients is performed. They were all male patients with a mean age of 40.65±2.10 (range 25-56) years. All patients had used "Krokodil" in the past (mean 27.4±3.9 months, range 5-72 months) (Table) and all of them had stopped its use a minimum of 1 month before surgery. Drug withdrawal period was 5.1±1 months (range 1-15 months). Involvement of maxilla was found in 1 patient, mandible in 10, both jaws in 6 patients. All patients had undergone radical surgery after minimum of one month of drug withdrawal [*Poghosyan Yu et al., 2014*]. During

Table

Summary of results of "Krokodil" drug-related jaw osteonecrosis patients

No	Age (years)	Involved jaw	Duration of "Krokodil" use (months)	Drug withdrawal period (months)	Onset of disease (months)	Presence of demarcation or sequestrum formation	C-terminal telopeptide *ng/ml*
1	52	Max Mand	36	2	20 10	demarcation No	0.142
2	56	Mand	24	14	5	No	0.208
3	31	Mand	24	5	3	No	0.130
4	43	Mand	20	3	5	No	0.121
5	40	Max Mand	5	3	6 5	No	0.121
6	34	Mand	12	5	8	No	0.115
7	41	Mand	18	1	6	No	0.108
8	29	Max Mand	24	1	6 12	No	0.089
9	37	Mand	48	6	7	No	0.078
10	43	Mand	24	2	12	No	0.076
11	48	Mand	36	15	15	seqestrum	0.992
12	25	Mand	18	5	2	seqestrum	0.981
13	51	Max Mand	36	4	6 24	seqestrum demarcation	0.481
14	33	Max Mand	8	4	5 6	seqestrum demarcation	0.405
15	43	Max Mand	72	6	48 24	demarcation demarcation	0.307
16	37	Max	36	7	3	seqestrum	0.290
17	48	Mand	24	3	8	demarcation	0.202

Notes: *max – maxilla, mand – mandible, NO -absence of demarcation or sequestrum.*

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surgeries osteonecrosis zone demarcation or sequestrum formation was determined. Then all patients were divided into two groups: I group – patients without signs of demarcation or sequestrum formation, II group – patients with osteonecrosis zone demarcation or sequestrum formation. Nine patients were included in I group (patient No 1 was included in II group), 8 patients – in II group.

In all patients serum C-terminal telopeptide tests were performed by ELECSYS 2010 (Roche Diagnostics, USA) electrochemiluminescence analyzer.

Compliance with ethical standards: Informed consent was obtained from all patients in this study.

IBM SPSS Statistics 20 was used for statistical analysis. Data are expressed as means ± SEM. T-test for independent groups was used to determine the difference of mean levels of C-terminal telopeptide in I and II group. Spearman's correlation test was run to determine the relationship between the mean level of C-terminal telopeptide and the presence of demarcation or sequestrum formation.

RESULTS AND DISCUSSION

In I group mean level of C-terminal telopeptide was 0.116±0.013 *ng/ml* (range 0.076-0.208 *ng/ml*), in II group it was significantly higher (t=3.029, p=0.019) at 0.475±0.118 *ng/ml* (range 0.142-0.992 *ng/ml*). There was a very strong, positive correlation between the mean level of C-terminal telopeptide and the presence of demarcation or sequestrum formation, which was statistically significant (r_s=0.818, p<0.0001).

In our study, decreased level of serum C-terminal telopeptide is found in I group patients. This shows the decreased bone turnover, which is the result of "Krokodil" use. Thus, "Krokodil" drug has anti-resorptive effect on bone tissue. This means that jaw osteonecrosis in "Krokodil" abusers is a new type of medication-related osteonecrosis of the jaw. The absence of necrotic bone demarcation is explained by reduced bone turnover due to anti-resorptive effect of "Krokodil".

Increased level of serum C-terminal telopeptide is found in II group patients. Its high level indicates the improved bone turnover. This makes possible the osteonecrosis zone demarcation and sequestrum formation (Fig. 2). Statistically significant positive correlation is found between the mean level of C-terminal telopeptide and the presence of demarcation or sequestrum formation. Only in one patient, with C-terminal telopeptide level higher than 0.150 *ng/ml* (minimal risk group according to R. Marx and co-authors (2007)), necrotic bone demarcation was not found. This shows that C-terminal telopeptide level is a predicting factor for visually identification of necrotic bone margins during surgery.

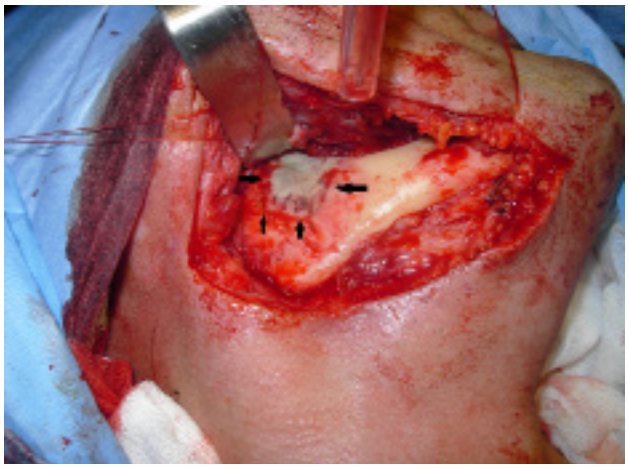

Figure 2. *"Krokodil" drug-addicted patient with osteonecrosis of right ramus of mandible. Demarcation line is shown by black arrows*

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