

MANAGEMENT OF KROKODIL/ DESOMORPHINE-INDUCED OSTEONECROSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Krokodil is a low-cost alternative to heroin which was first introduced in Russia and Ukraine and later spread to the rest of the world. Its main ingredient is desomorphine – a strong opioid with great analgesic potential. Its use has been associated with severe local and systemic damage, including osteonecrosis of the facial bones. This systematic review aims to determine whether radical bone surgery ensures uneventful healing with high success rates for patients with krokodil/desomorphine-induced osteonecrosis of the jaws. In addition, the distribution of the affected jaws, the triggering factors for osteonecrosis development, and the reported treatment modalities were also included in the analysis. An advanced search for case series, case reports, and clinical trials in English was conducted on 04 February 2025 in the Web of Science, Scopus, and PubMed databases. Following the PRISMA guidelines, 75 records were screened and evaluated, identifying 12 articles eligible for inclusion in this systematic review. It was found that further epidemiological research is necessary to define the osteonecrosis distribution according to the jaw. The appropriate treatment includes radical bone surgery within healthy tissues. Most of the cases presented uneventful healing (49) but there were still many reports of osteonecrosis recurrence (16) and other postoperative complications (11). The main triggering factor for krokodil-induced osteonecrosis of the jaws was tooth extraction. Other predisposing factors included local trauma, poor oral hygiene, periodontal disease, and periapical lesions. Further research is necessary to identify the success rate of tissue regeneration procedures in such patients.

Key words: krokodil, desomorphine, osteonecrosis

INTRODUCTION

At the beginning of the 20th century, a low-cost alternative to heroin was introduced in Russia and Ukraine and then spread to the other neighboring countries and later to the rest of Europe and the USA [1, 2]. The drug was called “krokodil” (the Russian word for crocodile) due to the clinical view of the skin lesions associated with its continuous use and resembling crocodile skin [3, 4]. The drug is produced at home using codeine, which was taken over-the-counter in Russia until 2012, iodine, red phosphorous, gasoline, and other starting substances [1, 5]. The main resulting product is desomorphine – an opiate that has great analgesic potential.

The most common administration route is

intravenous; thus, its use is usually associated with thrombophlebitis, limb ulcers, discolorations, and in advanced stages – gangrene, necrosis, and amputations. Other symptoms include systemic damage (endomyocarditis, kidney and renal failure, meningitis, etc.) and neurotoxicity (cognitive function loss, hallucinations, difficulties in memory, speech, and so on) [1]. An increasing number of cases with jaw osteonecrosis has also been reported [6-18], presented by pain, bone exposure (in up to 92% of the cases), soft tissue inflammation and dehiscences, mucous and skin fistulas, and so on [7]. This osteonecrosis resembles phosphorous jaw osteomyelitis, also known as “phossy jaw”. The main characteristics of this condition are

its prolonged course, resistance to conventional antibiotic therapy, and rapid spread to the neighboring tissues, leading to severe facial deformities. The treatment includes radical surgical resections with borders of healthy tissues with immediate or delayed titanium implant placement to replace the missing bone segments [6]. A key prerequisite for treatment success is prolonged preoperative drug withdrawal and its definite cessation [7].

Despite the severe tissue destruction caused by krokodil, a lot of people do not seek medical help or do it at late stages [1], leading to severe tissue damage or even fatal endings.

This study aims to determine whether radical bone surgery ensures uneventful healing with high success rates for patients with krokodil/desomorphine-induced osteonecrosis of the jaws. In addition, the distribution of the affected jaws, the triggering factors for osteonecrosis development, and the reported treatment modalities were also included in the analysis.

MATERIALS AND METHODS

The review question followed the PIO framework where “P” stands for patients (with a history of krokodil/ desomorphine abuse and

bone necrosis), “I” stands for intervention (radical bone surgery), and “O” stands for outcome (healing without recurrence): Is radical bone surgery (I) in patients with a history of krokodil/ desomorphine osteonecrosis (P) effective for uneventful healing without recurrence (O)?

The selected Inclusion criteria were: 1. Case reports, case series, and clinical trials; 2. Studies discussing krokodil/desomorphine-induced osteonecrosis and its management; 3. Studies in English. Accordingly, the exclusion criteria were: 1. Review articles, preclinical trials, books, and abstracts; 2. Studies not discussing krokodil/desomorphine-induced osteonecrosis and its management; 3. Articles not written in English.

The systematic review was structured in accordance with **the PRISMA guidelines** [19, 20]. The registration protocol in the Open Science Framework can be found at <https://doi.org/10.17605/OSF.IO/PGUWK>.

On 04/02/2025, an advanced search in the selected databases (Web of Science, Scopus, and PubMed) was conducted using the document type and English language as filters and the following keywords: krokodil, desomorphine, and necrosis (also a MeSH term) (Figure 1).

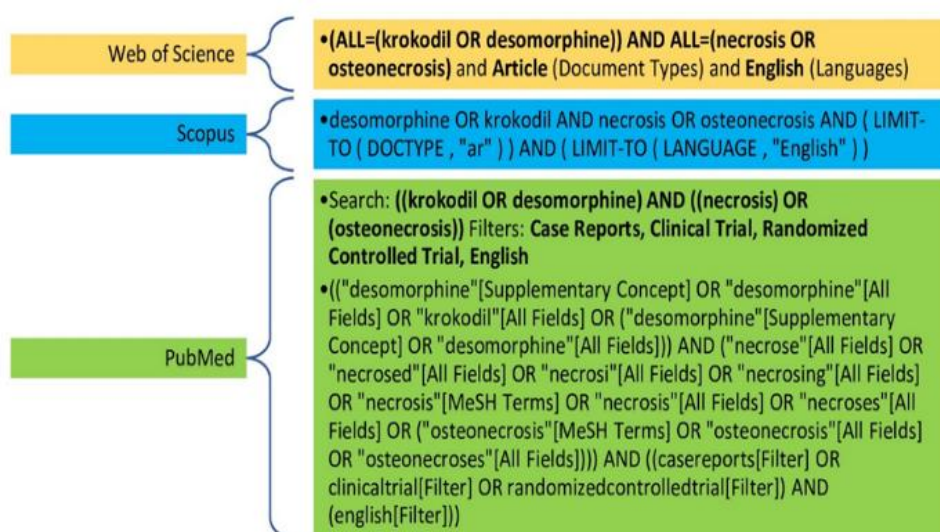


Figure 1. The query strings used in each database.

The results were exported, screened, and processed in MS Excel (2016) by two reviewers (E.S. and D.D.) independently from each other. Following duplicate records removal, the titles and abstracts were initially screened, and the studies, that met the eligibility criteria, were further evaluated. The information retrieved for the studies included: study design (number of cases), affected bone, triggering factors for osteonecrosis development, healing, and regeneration procedures.

The two reviewers independently assessed the studies for risk of bias using the JBI critical appraisal tool [21, 22]. They resolved disagreements by analyzing and discussing them until a consensus was reached.

RESULTS AND DISCUSSIONS

The initial search identified 75 potentially relevant articles. The duplicates (20 records) were removed and the remaining 55 studies were subjected to the eligibility criteria. In the end, 12 articles were included in this review (Figure 2). Their characteristics are presented in Table 1. Figure 3 displays the quality assessment.

Table 1. Studies included in the systematic review.

Ref	Study Design	Number of cases	Affected bone	Triggering factor	Drug Withdrawal	Surgical Treatment	Healing	Regeneration procedures used
8	Case report	1	Both jaws	Tooth extraction	8 months	Bone resection in healthy tissues	Uneventful (3-year follow-up)	Not reported
9	Case report	1	Upper jaw	Tooth extraction	5 months	Necrectomy/ sequestrectomy with a 0.5 cm border of healthy tissues	Uneventful (2-month follow-up)	Not reported
10	Case series Case report 1	3	Upper jaw, right midfacial area	Tooth extraction	14 months	Resection of the necrotic bone with a 5 mm border of healthy tissues; closure of OAC with local flaps	OAC persisted after 8 months with no signs of osteonecrosis recurrence (8-month follow-up)	Not reported

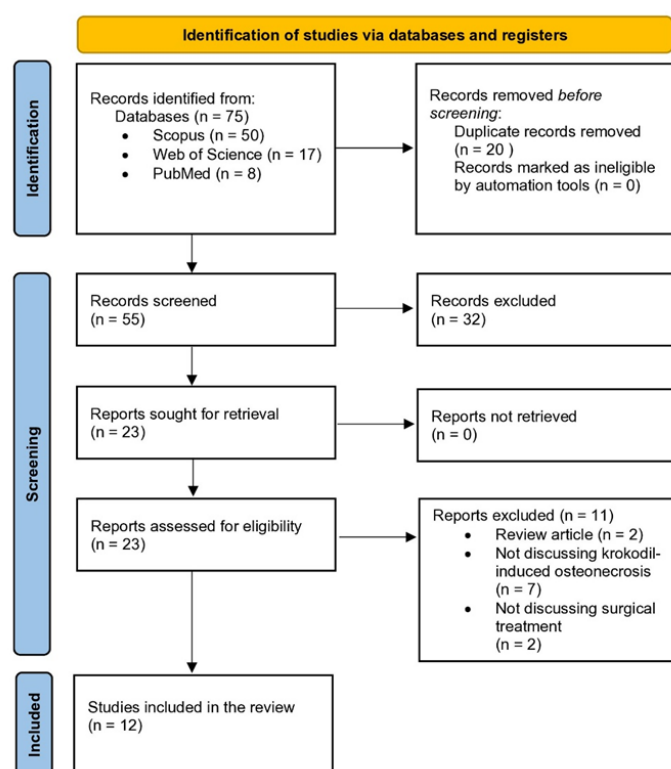


Figure 2. The PRISMA flowchart.

	Case report 2		Left midfacial area, upper jaw	Recurrence of maxillary osteonecrosis	12 months	Resection of the necrotic bone with a 5 mm border of healthy tissues;	The osteonecrosis recurred along with a skin defect exceeding the size of the soft tissue defect before the surgery.	Not reported
	Case report 3		Right midfacial area, upper jaw, and alveolar ridge	Tooth extraction	8 months	Alveolar bone resection; closure of OAC with BFP	Uneventful (7-month follow-up)	Not reported
7	Case series	17	Upper jaw – 1 Lower jaw – 10 Both jaws - 6	Not reported	1-15 months	Radical surgery	Not reported	Not reported
11	Case series	24	Distal regions of the lower jaw	Tooth extraction (21 cases) or osteonecrosis recurrence (3 cases)	10-48 months	Resection in healthy tissues (0.5 cm border) and tension-free closure of the soft tissues using local full-thickness flaps (15 cases) or double-layered muscular (mylohyoid muscle) and full-thickness flaps (9 cases)	There was no recurrence in the second group. In one patient there was temporary lingual nerve damage. In the first group, there were soft tissue dehiscences in 9 patients. After healing on secondary intention, osteonecrosis recurrence was registered in 7 patients.	Not reported
15	Case series	50	The upper jaw, zygomatic bone, floor of the orbit	Tooth extraction and other non-specified factors	≤ 3 months	Bone resections (partial or total resection of the maxilla ± the zygomatic bone; ± the floor of the orbit with 0.5 -1 cm borders of healthy tissues	Uneventful for patients following the instructions; in patients with recurrent drug use and poor oral hygiene – deterioration of the condition; in 3 patients – death due to an overdose	Not reported
16	Case series	40	The upper jaw – 11 cases, the lower jaw – 21 cases, or both – 8 cases	Tooth extraction in most cases, not fitting dentures, periapical pathology, trauma, periodontal disease, poor oral hygiene	≥ 1 month	In patients with drug withdrawal less than 1 month – conservative therapy In patients with at least 1 month of withdrawal – radical surgery with a 0.5 cm border in healthy	Recurrence in 8 out of 40 cases	Not reported

						tissues – necrectomy, sequestrectomy, jaw resections, flapless closure of OACs (when present), and conservative therapy		
17	Case report	1	Left upper jaw, sphenoid bone, zygomatic bone, and lateral orbital rim	Recurrence of osteonecrosis	36 months	Necrectomy and bone resections	Uneventful (10- month follow-up)	Not reported
18	Case report	1	The right side of the lower jaw	Not reported	No (intraoral submucous injections)	Immunomodulati on therapy, partial jaw resection with a border of healthy tissues, conservative therapy	Uneventful	Reconstruction of the jaw with titanium implant
13	Case series	6	Distal areas of the upper jaw	Tooth extraction	1-24 months	Radical resection with 0.5 border of healthy tissues or until bleeding was found when there was no demarcation; closure of the OAC with a BFP	Uneventful (8-12- month follow-up)	Not reported
14	Case series	5	Distal areas of the lower jaw	Tooth extraction – 4 cases; Osteonecrosis recurrence – 1 case.	6-24	Radical resection with 0.5 border of healthy tissues or until bleeding was found when there was no demarcation; closure of the defect with local flaps and BFP	Uneventful (12-16- month follow-up)	Not reported
12	Case report	1	Right distal area of the lower jaw (adjacent to tooth #45)	Spontaneous recurrence	15 months	Resection in healthy tissues and coverage with sublingual gland flap	Uneventful (6-month follow up)	Not reported

OAC – oroantral communication; BFP – buccal fat pad.

Risk of Bias Assessment – Case Reports							
QUESTION	Hakobyan 2017 [8]	Hakobyan 2017 [9]	Hakobyan 2024 [12]	Poghosyan 2022 [17]	Ramishvili 2022 [18]		
1	YES	YES	YES	YES	YES		
2	YES	YES	YES	NO	YES		
3	YES	YES	YES	YES	YES		
4	UNCLEAR	YES	YES	YES	YES		
5	YES	YES	YES	YES	YES		
6	YES	YES	YES	YES	YES		
7	NO	NO	NO	NO	NO		
8	YES	YES	YES	YES	YES		
SCORE	6	7	7	6	7		
RISK OF BIAS	MEDIUM	LOW	LOW	MEDIUM	LOW		
Questions: 1. Were patient’s demographic characteristics clearly described? 2. Was the patient’s history clearly described and presented as a timeline? 3. Was the current clinical condition of the patient on presentation clearly described? 4. Were diagnostic tests or assessment methods and the results clearly described? 5. Was the intervention(s) or treatment procedure(s) clearly described? 6. Was the post-intervention clinical condition clearly described? 7. Were adverse events (harms) or unanticipated events identified and described? 8. Does the case report provide takeaway lessons?							
Risk of Bias Assessment – Case Series							
QUESTION	Hakobyan 2017 [7]	Hakobyan 2021 [11]	Ispiryan 2023 [15]	Poghosyan 2014 [16]	Hakobyan 2018 [13]	Hakobyan 2024 [14]	Hakobyan 2019 [10]
1	YES	YES	YES	YES	YES	YES	YES
2	YES	UNCLEAR	YES	YES	YES	YES	YES
3	YES	UNCLEAR	YES	YES	YES	YES	YES
4	UNCLEAR	UNCLEAR	YES	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
5	UNCLEAR	UNCLEAR	YES	YES	UNCLEAR	UNCLEAR	UNCLEAR
6	YES	YES	YES	YES	YES	YES	UNCLEAR
7	NO	YES	YES	YES	YES	YES	YES
8	NO	YES	YES	YES	YES	YES	YES
9	NO	YES	YES	YES	NO	YES	YES
10	YES	YES	YES	YES	YES	YES	UNCLEAR
SCORE	5	7	10	9	7	8	6
RISK OF BIAS	M	L	L	L	L	L	M
Questions: 1. Were there clear criteria for inclusion in the case series? 2. Was the condition measured in a standard, reliable way for all participants included in the case series? 3. Were valid methods used for identification of the condition for all participants included in the case series? 4. Did the case series have consecutive inclusion of participants? 5. Did the case series have complete inclusion of participants? 6. Was there clear reporting of the demographics of the participants in the study? 7. Was there clear reporting of clinical information of the participants? 8. Were the outcomes or follow up results of cases clearly reported? 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? 10. Was statistical analysis appropriate?							

Figure 3. Quality assessment of the included articles

From the included studies, osteonecrosis was presented in the upper jaw in 73 cases (49%), in the lower jaw – in 62 cases (41%), and both jaws were affected in 15 cases (10%) (Figure 4). In 30 cases, tooth extraction was identified as a triggering factor for jaw necrosis. In other 90 cases, it was stated that the most common reason was tooth extraction, followed by different factors, such as not fitting dentures, periapical pathology, trauma,

periodontal disease, and poor oral hygiene. In 6 cases, the reason was osteonecrosis recurrence. The treatment of choice, confirmed by the results from the included studies, is radical surgery (necrectomy and bone resections) with a border of healthy tissues. Only one of the studies discussed the subsequent tissue replacement following the bone resection [18]. Some of the case series did not specify the success and recurrence

rates. Uneventful healing was reported in 49 cases, while necrosis recurrence was reported in 16 cases. Other postoperative complications included soft tissue dehiscences (9 cases), oroantral communication development (OAC) (1 case), and temporary lingual nerve damage (1 case) (Figure 5). Three death cases were reported due to an overdose.

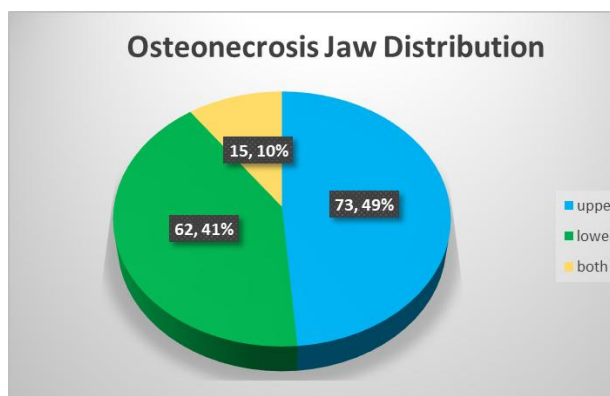


Figure 4. Distribution of krokodil-induced necrosis according to the jaw.

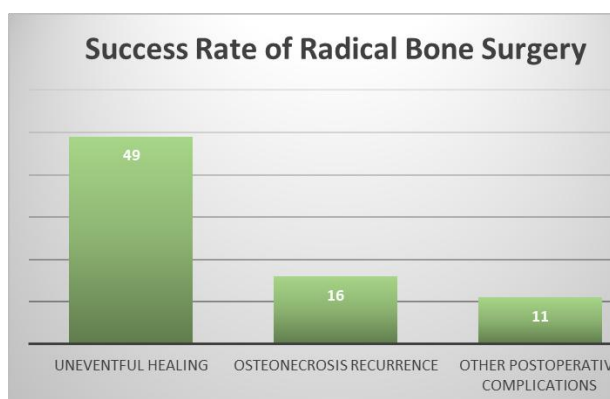


Figure 5. The success rate of jaw resection in healthy tissues.

Although the presented studies indicated that krokodil-induced osteonecrosis most commonly affected the upper jaw (49% vs. 41% in the lower jaw), Babkova et al. [6] found that mandibular desomorphine-induced osteonecrosis in 49 cases, maxillary osteonecrosis in 34 cases and in 25 cases both jaws were affected. This study was excluded from the analysis because it did not discuss the

management of the condition. Furthermore, according to a systematic review by van Kempen and Brand, the mandible was reported to be more commonly affected than the maxilla [2]. This phenomenon is usually explained by some anatomical features of the lower jaw (higher density, larger amount of compact bone, and worse blood supply than the upper jaw) and has been discussed in the ethiopathogenesis of jaw osteomyelitis, osteoradionecrosis, and medication-related osteonecrosis of the jaw [23]. When presented in the mandible, the krokodil-induced osteonecrosis usually affects the jaw body and angles. Sometimes the mandibular canal and the inferior alveolar nerve can be involved [6].

The presented study heterogeneity necessitates further epidemiological research to determine the incidence of krokodil-related osteonecrosis and the distribution of the affected bones.

It was evident that the most common triggering factor for jaw osteonecrosis was tooth extraction. The onset of the destruction is usually between 12-18 months following the tooth removal [2]. Other important predisposing factors include not well-fitted removable dentures and fixed prosthetic restorations, which cause trauma and plaque accumulation and, thus, contribute to the development of periodontal disease [24-26]. Periapical lesions have also been associated with a higher risk for osteonecrosis in these patients.

In cases of MRONJ, including krokodil-induced osteonecrosis, the pathogenesis can be related to inhibited bone remodeling processes and angiogenesis, infections and immune deficiencies, toxicity, and trauma. The bone regenerative capacity can be evaluated using histological and histomorphometric evaluation [27-29]. Bone deficiency in the maxillofacial area has been associated with different etiological factors (congenital defects, traumas, infections, tumors, and bone

metastasis) [30, 31]. Infections often cause osteolysis as the purulent discharge passes through the structures in the direction of less tissue resistance [32].

The treatment of desomorphine-induced necrosis is complex. It includes bone resections and reconstructive surgery and requires collaboration between narcologists, infectious disease specialists, maxillofacial surgeons, vascular surgeons, orthopedic surgeons, internists, dentists, and so on.

The recommended surgical method is radical bone surgery – a resection with a 0.5 cm border of healthy tissues. It must be noted that the surgery is followed by postoperative conservative treatment with antibiotics and antiseptics. Uneventful healing was registered in 49 cases, osteonecrosis recurrence – in 16 cases, and 11 cases presented other postoperative complications, such as soft tissue dehiscence, development of an OAC, and temporary nerve damages. In most cases of recurrence, it was associated with recurrent drug use and poor oral hygiene [11]. In 2021 Hakobyan and Poghosyan gave the following recommendations for successful surgical treatment: if there is a clear demarcation between necrotic and healthy bone, the resection of the non-vital bone is performed with extension of the bone removal of 5 mm in all directions; if there is no demarcation, the resection is performed until a vital bone is reached, which can be recognized by the bleeding. Other key prerequisites for treatment success are drug use cessation (with at least 1 month of withdrawal preoperatively) and tension-free closure of the soft tissues [11].

The subsequent rehabilitation procedure was reported in only one of the included 138 cases. The main reason for that is probably that the patients suffer from addiction and

withdrawal is required for successful implant therapy, bone and soft tissue grafting and plasty, guided regeneration, and other augmentation procedures. The treatment planning requires appropriate radiological examinations – X-rays, CT, and CBCT. The latter has been considered the method of choice for the evaluation of the jaw bones and the alveolar ridges [33, 34]. Nowadays, numerous new methods for jaw reconstructions, flap reconstructions, and tissue augmentation have been suggested [35]. Novel materials have been introduced, unraveling improved material properties and potential for drug delivery, scaffolding, and tissue engineering to meet the patient's needs [36-42]. Recently novel methods for the closure of OAC have been introduced, reducing the undesired tissue deficiency caused by conventional plasty techniques [43, 44]. In 2017 Hakobyan and Poghosyan reported two cases of spontaneous lower jaw bone recovery after jaw resection and spontaneous OAC closure following [8, 9]. However, further evidence is necessary to validate these phenomena.

The limitation of this study is that the distribution of the affected jaws was based only on the articles meeting the eligibility criteria. Further research is necessary to identify all registered reports on krokodil-induced jaw necrosis and determine the exact frequencies, and identify the possible correlations between the treatment success and the drug use period on the one hand and the drug withdrawal period on the other hand. Furthermore, the included research does not present the methods for further replacement of the missing tissues following the resections. Future studies should discuss the rehabilitation of these patients.

condition that requires radical surgical interventions following drug withdrawal.

CONCLUSIONS

1. Krokodil/desomorphine-induced osteonecrosis of the jaws is a mutilating

2. Tooth extraction was reported to be the most important triggering factor. Other

- predisposing factors are local trauma, poor oral hygiene, periodontal disease, and periapical lesions.
3. Osteonecrosis recurrence after resection in healthy tissues is usually associated with recurrent drug use and poor oral hygiene.
 4. Further research is necessary to identify the distribution of the affected facial bones, the methods for restoration of the missing tissues, and the success rate of the regeneration procedures in such patients.

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