Effects of krokodil (desomorphine) use on oral health – a systematic review

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Key points

- The narcotic drug krokodil is a semi-synthetic drug used as a cheap alternative to heroin; with its active ingredient desomorphine it is a highly addictive and destructive drug mainly used in Russia and Eastern Europe.
- Osteonecrosis of the maxillofacial bones is a serious and mutilating oral side effect associated with krokodil use.
- Other oral aspects associated with krokodil use include mucosal changes, high risk of caries and periodontitis.
- The use of krokodil drug can interfere with dental and oral- and maxillofacial treatment.

Abstract

Introduction The narcotic drug krokodil is a semi-synthetic drug used as a cheap alternative to heroin. With its active ingredient desomorphine it is a highly addictive and destructive drug mainly used in Russia and Eastern Europe. Relatively little is known about the physical effects of krokodil. With this review we present more insight into oral health problems associated with krokodil use and how the use of this drug could influence dental and oral- and maxillofacial treatment.

Methods The online electronic databases Pubmed, Web of Science, Cochrane Library and Google scholar were searched for articles concerning desomorphine or krokodil and oral side effects or pathology. Reference lists of included articles were manually screened for additional publications.

Results Thirteen articles were included in this review. In total 684 patients were described in the included publications, mainly retrospective clinical case series and case reports. Eleven studies reported on osteonecrosis of the jaw and two studies reported on other physical and oral side effects associated with desomorphine abuse.

Conclusion Osteonecrosis of the maxillofacial bones is a serious and mutilating oral side effect associated with krokodil use. Other oral aspects associated with its use include mucosal changes, high risk of caries and periodontitis. In addition, physical effects of the drug, which indirectly can affect oral health, have also been described. The use of the drug krokodil can interfere with dental and oral- and maxillofacial treatment.

Introduction

Krokodil is a semi-synthetic narcotic drug used as a cheap alternative to heroin. It is easy to synthesise, with low costs and often homemade. Because it is homemade it is often contaminated with other substances.[1] Krokodil is most commonly used in Eastern Europe and Russia, given that the codeine pills necessary for production of krokodil are freely available at pharmacies. However, recently, the number of cases associated with krokodil use has increased in other regions of Europe and America.[2,3]

Krokodil is made using codeine, gasoline, iodine and red phosphorous (from matchboxes). By combining these substances, a drug is created that contains the active analgesic substance desomorphine. Desomorphine (4,5-a-epoxy-17-methylmorphinan-3-ol) is an opiate drug used as alternative pain medication for morphine since 1934. Desomorphine is ten times as potent as morphine, making this substance highly addictive.[4] In addition to desomorphine, krokodil also contains substances such as 3,6-dideoxy-dihydromorphine, morphinan-4,5-epoxy-3-ol and traces of codeine.

Krokodil is mainly administered intravenously but can also be administered intramuscularly or taken orally. After injecting the drug, necrosis of the skin and a black-green discolouration of the skin may occur, from which the name krokodil is derived as it resembles a crocodile's skin. In addition to cutaneous side effects, many other physical side effects have been reported such as nausea, dyspnea,[2,3] hyperthermia, tachycardia state, fear, hallucinations[5] and endomyocarditis.[3] The introduction of highly toxic components into the bloodstream could potentially also yield devastating effects on the maxillofacial area.

Mechanism of action

Desomorphine is an opioid that can cross the blood-brain barrier and bind to opioid receptors in the central nervous system. It binds primarily to the mu-opioid receptors, but can also bind to the mu, kappa- and delta-receptors. Shortly after injecting desomorphine, effects such as analgesia, sedation, gastro-intestinal dysmotility and euphoria will occur. Other

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reported effects of 'desomorphine' are miosis, flushing, paresthesia, constipation, nausea and vomiting. Desomorphine can also provoke allergic reactions, seizures and respiratory depression.[1] Desomorphine has a faster onset and shorter half-life than morphine, but desomorphine has a ten times higher analgesic effect than morphine.[4] This extreme analgesic effect and the dependence to the drug might be related to the affinity for the mu-receptors.[1]

Aim of this research

Relatively little is known about the physical effects of krokodil. In this review we present an insight into oral health problems associated with krokodil use and how the use of this drug could affect dental and oromaxillofacial treatment. For this review, literature was systematically searched to describe evidence-based knowledge and the relationship between the use of krokodil and oral health. The aim of this systematic review was to provide an overview of how krokodil (desomorphine) potentially affects oral health.

Material and methods

The online electronic databases PubMed, Web of Science, Google Scholar and Cochrane Library were searched for articles using keywords related to krokodil (desomorphine) use. Reference lists of included articles were manually searched for additional relevant articles, which could not be found through conventional electronic searches. One investigator screened potential articles on eligibility based on abstract and full text. Oral health problems directly associated with krokodil (desomorphine) were investigated. Furthermore, indirect general effects due to use of this drug that could affect oral health, were also part of this research.

An initial search was conducted using the keywords: dental, desomorphine, drug, krokodil, oral health, osteonecrosis.

("desomorphine"[All Fields] OR "desomorphine"[All Fields] OR "krokodil"[All Fields]) AND drug[All Fields])

("(krokodil drug)[All Fields] OR "desomorphine"[All Fields]) AND "oral health" [All Fields])

("(krokodil drug)[All Fields] OR "desomorphine"[All Fields]) AND "dental" [All Fields])

The online electronical search resulted in 337 records. The PRISMA flowchart (Fig. 1) illustrates the process of study selection.

Inclusion and exclusion criteria

For this review human studies like cohort studies, case series, case control studies, cross-sectional studies, reviews and clinical trials researching physical effects which could affect oral health of krokodil or desomorphine were considered for evaluation. Since the drug is mainly used in Eastern Europe and Russia, there was no restriction on language.

Articles without clear case-descriptions had to be excluded, such as review articles. Records containing expert opinion only were also excluded. Only studies in humans were included. These criteria resulted in 13 included scientific papers with clinical outcome measures from cohort studies, retrospective case series or case reports.

Results

Table 1 presents a concise overview of the characteristics of the included research articles. Most oral effects of krokodil come from case series. Due to the large heterogeneity of the clinical outcome measures in these publications, the data will be presented by examined aspect.

Osteonecrosis of the jaw

One of the most frequently reported oral side effects associated with krokodil use is osteonecrosis of the maxillofacial bones. In 11 of the included studies, osteonecrosis of maxillofacial bones was reported. This clinically presents as dim greyish exposed bone, with a yellowish shade covered with greyish plaque.[6,7,8,9,10,11] The exposed area of necrotic bone varies from one to three dental sockets up to the whole alveolar process.[11] A decrease in the size of the jaws was frequently noticed on panoramic radiographs, due to the presence of osteonecrosis. In 16.5% there was no significant change in the size of the jaws. In 20% of the reported patients an increase in the size of the mandible was determined due to periostitis.[12]

In most of the articles describing osteonecrosis of the maxillofacial bones, the mandible was more frequently affected than the maxilla.[6,7,11,12,13,14,15,16] In approximately half of the cases osteonecrosis was present in the mandible. Osteonecrosis is mainly present in the body or angle of the mandible, and the mandibular nerve canal may be involved.[12] In some cases osteosclerosis was

Fig. 1 PRISMA flow chart

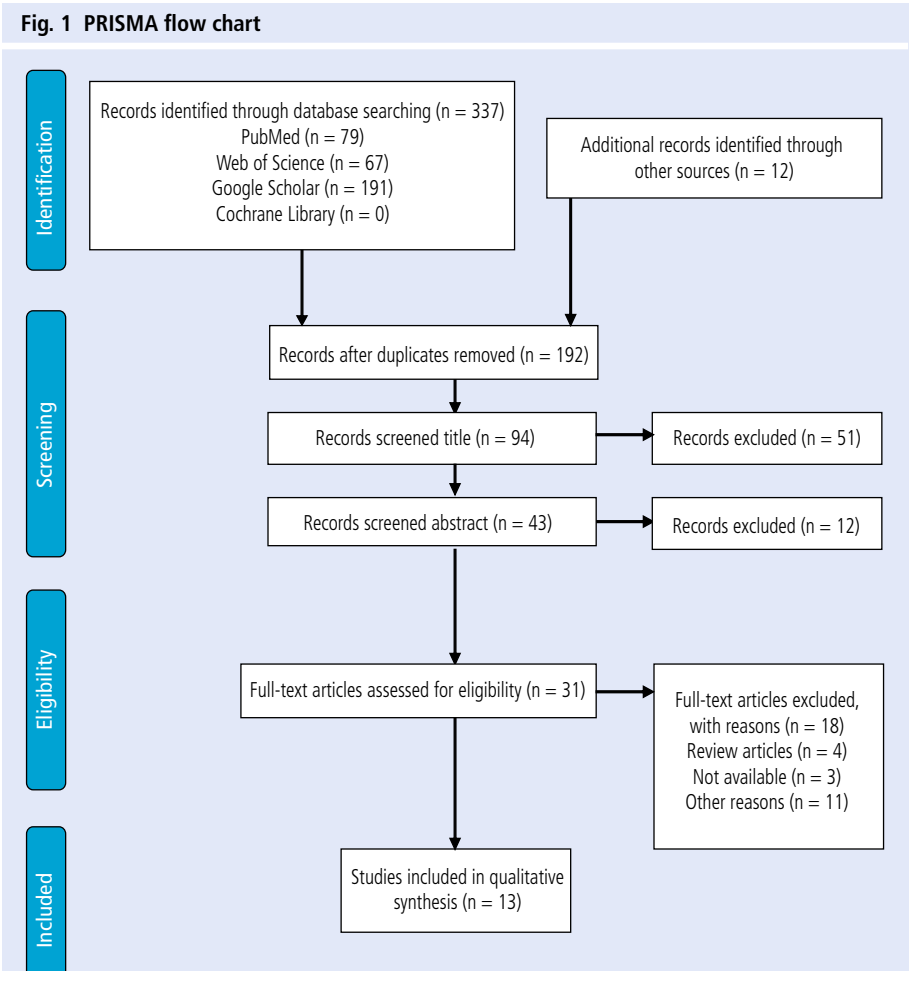

Table 1 Characteristics of included studies (cont. on page 809)

Reference	Study design	Study population baseline characteristics	Characteristics outcomes
Babkova A (2014) (Radiological diagnosis of facial osteonecrosis in patients taking desomorphine)[6]	Case-series	n = 135	Exposed alveolar processes of the jaws, empty tooth sockets, gum recession, increased volume of soft tissue, maxillary sinusitis. Formation of extensive zones of sequestration, and osteoporotic and osteosclerotic areas alternating in the bone tissue. Destruction of the body of the mandible Widened periodontal fissure with sclerotic end plates: 60 (45%). Pathological mandible fracture: 14 patients (11%) In bone scintigraphy excessive accumulation of radiopharmaceutical in orbital- and zygomatic region
Babkova A (2015b) (Complex radiological diagnostics of osteonecrosis in desomorphine-dependent patients)[12]	Case-series	n = 85 (78 male, 7 female) Mean age: 29 (18–40) Time of abuse (months): (21–20)	Maxilla: 25 patients (31%). Mandible: 36 patients (45.5%). Mandible fracture: 19 patients (22%). Both jaws: 18 patients (23%). Sequestras in: 35 (41%). Process wall of maxillary sinuses, palatal, orbital- and zygomatic region affected Changes in periodontal gap: 56 (66%). Periostitis: 31 (36%). Decrease in size due to presence of pronounced focus of osteocnecrosis: 54 (63.5%). Significant change in jaw size not identified: 14 (16.5%)
Babkova A (2015a) (Radiological diagnosis of osteonecrosis in desomorphine-associated patients)[7]	Case-series	n = 165 Age (range): (19–49) Range months of abuse: (2–92) Hepatitis C: 164 (99.4%), HIV: 24 (14.5%), TBC: 4 (2.4%)	Widened periodontal fissure with sclerotic end plates: 75 patients (45%). Massive diffuse periosteal deposits mandible: 52 (31.5%). Mandible fracture: 24 (14.5%). Alterations upper-jaw maxillary sinusitis: 13 (8%). Recession gum, exposed alveolar process mandible, increased soft tissue volume In bone scintigraphy excessive accumulation of radiopharmaceutical in orbital region, zygomatical region and nasal region. Massive bone destruction distal mandible, right and left ramus mandible, body mandible, alveolar part of the mandible, wide areas of bone sequestration
Babkova A (2017) (Complex radiological diagnosis of osteonecrosis in patients taking desomorphine in the pre- and postoperative periods)[13]	Case-series	n = 165 Age (range): (18–51) Time of abuse (months): 18–96 Hepatitis C: 159 (96,4%), HIV: 26 (15,8%), TBC: 5 (3,0%)	Massive diffuse periosteal deposits predominantly in mandible: 97 patients (59%). Maxilla: 39 patients (24%). Widened periodontal fissure with sclerotic end plates: 76 patients (46%). Pathological mandible fracture: 38 cases (23%). Gum recession, exposed alveolar processes of the jaws, open areas of bone tissue resistant to standard pharmacological treatment. Empty tooth sockets 100%. Increased volume of soft tissue. In bone scintigraphy excessive accumulation of radiopharmaceutical in orbital region, zygomatic region and nasal region
Basin (2012) (Osteonecrosis of the facial skeleton bones in persons with narcotic dependence (clinic, diagnostics, treatment)[15]	Case-series	n = 45 (35 male, 10 female) Age (range): (22–42) Hepatitis C: 44 (97.9%), HIV: 7 (15.5%), TBC: 3 (6.6%)	Mandible: 25 patients (55.6%). Maxilla: 5 patients (11.1%). Both jaws and/or facial bones: 15 patients (33.3%) Pathological jaw fracture: 7 (15.6%). Persistent purulent discharge with smell, progress gum recession, presence granulation tissue, increased bone density, Massive periosteal growths of newly formed bone tissue
Hakobyan (2012) (The state of oral cavity in drug addicted patients with jaw osteonecrosis who use the drug 'Crocodile' [desomorphine])[14]	Case-series	n = 21 (all male) Age (range): (33–50) Mean months of abuse: 17,24 ± 1.87 (2–36) Hepatitis C: 20 (95.2%), HIV: 1 (4.8%)	Maxilla: 5 patients (23.8%). Mandible: 11 patients (52.4%). Both jaws: 5 patients (23.8%). Resorption of interdental septa to 1/3 of height: 6 (35.5%). Resorption of interdental septa to 2/3 of height: 8 (47.1%). Resorption of interdental septa more than 2/3 of height: 3 (17.6%). 61.9% of patients did not brush their teeth in for a year or more. Rest of patients brushed their teeth once a day, but not regularly Caries prevalence (100%). Periodontal disease: gingivitis (10.5%), periodontitis (89.5%)
Hakobyan K A (2017c) (C-terminal telopeptide level in 'krokodil' drug-related jaw osteonecrosis patients)[16]	Retrospective case study	n = 17 (all male) Mean age: 40.65 ± 2.10 (25–56) Mean time of abuse (months): 27.4 ± 3.9 (5–72)	Maxilla: 1 patient (5.9%). Mandible: 10 patients (58.8%). Both jaws: 6 patients (35.3%). No signs of demarcation or sequestrum formation: 9 patients (52.9%). Patients with osteonecrosis demarcation or sequestrum formation: 8 patients (47.0%). Demarcation in maxilla: 2 patients (11.8%). Demarcation in mandible: 4 patients (23.5%). Sequestrum in maxilla: 3 patients (17.6%). Sequestrum in mandible: 2 patients (11.8%)
Hakobyan K A (2017a) (Spontaneous bone formation after mandible segmental resection in 'krokodil' drug-related jaw osteonecrosis patient: case report)[8]	Case-report	n = 1 (male) Age: 48 Time of abuse (months): 18	Both jaws: 1 patient. Partial exposure of left maxilla. Total exposure of mental and distal parts mandible. Large sequestrum and sinus purulent discharge on maxilla. Sequestrum and thickened maxillary sinus floor. Mandible sequestrated angle to angle. On removed mandible, large newly formed bone zones were found due to chronic inflammation and ossifying periostitis
Hakobyan (2017b) (Spontaneous closure of bilateral oro-antral communication formed after maxillary partial resection in 'krokodil' drug related jaw osteonecrosis patient: case report)[9]	Case-report	n = 1 (male) Age: 40 Hepatitis C: 1 (100%) Mean time of abuse (months): 18	Partial exposure of the right maxilla. Radiographical total opacification of both maxillary sinuses. Clear demarcation line between vital and non-vital bony structures
Hakobyan (2018) (The use of buccal fat pad in surgical treatment of 'Krokodil' drug-related osteonecrosis of maxilla)[10]	Retrospective case-series	n = 6 (all male) Hepatitis C: 6 (100%) Mean time of abuse (months): 13 ± 1.8 (6–18)	Unilateral exposure of maxillary alveolar process: 5 patients (83,3%). Total involvement of maxillary alveolar process: 1 patient (16,6%). Clear demarcation of necrotic zone: 5 patients (83,3%). No signs of demarcation: 1 patient (16,6%). Clinical formed sequestrums: 2 patients (33,3%). Clear demarcation line between vital and non-vital bone: 3 patients (50%). No demarcation line or sequestrum formation: 1 patient (16,6%)

Table 1 Characteristics of included studies (cont. from page 808)

Reference	Study design	Study population baseline characteristics	Characteristics outcomes
Kwint (2013) (Gevaarlijke designer drug krokodil voor het eerst in Nederland gesignaleerd)[2]	Case-report	n = 1 (male) Age: 24	Redness and erosion of mucosa of the oral cavity and pharynx
Lemon (2013) Homemade heroin substitute causing hallucinations)[5]	Case-report	n = 1 (female) Age: 19	Dermatological lesions large scabs each 4–5 cm in diameter on her face Poor hygiene All teeth present, recent tooth discoloration
Poghosyan (2014) (Surgical treatment of jaw osteonecrosis in 'Krokodil' drug addicted patients)[11]	Case-series	n = 40 (39 male, 1 female) Mean age: 41 ± 1 (26–54) Hepatitis C: 37 (92,5%), Hepatitis B: 2 (5%), HIV: 1 (2,5%)	Maxilla: 11 patients (27.5%), Mandible: 21 patients (52,5%), Both jaws: 8 patients (20%) Oroantral communication in 8 (38%) Sequestra in 13 patients (23), Sequestrum in maxilla: 8 patients, Sequestrum in mandible: 5 patients

found in the coronary and condylar regions of the mandible.[12] Pathological mandible fractures were reported by five studies, varying from 11% to 23% of the reported patients investigated.[6,7,12,13,15] Due to this pathological fracture, displacement of bone fragments can lead to deformity of facial features.[12]

Osteonecrosis affects the maxilla in 5.9–31% of the patients investigated. In 23–35.3% both jaws and/or other maxillofacial bones such as the process wall of maxillary sinuses, palatal, orbital and zygomatic region are affected.[9,12] In scintigraphy, an excessive accumulation of radiopharmaceutical is reported in the orbital,[6,7,13] zygomatic[6,7,9,12,13] and nasal regions.

Whether sequestrum or demarcation of necrotic zones is found varies between studies and reported patients.[9] Hakobyan *et al.*[16] found that there was a strong positive correlation between the level of C-telopeptide and presence of demarcation or sequestrum formation. The absence of necrotic bone demarcation can be explained by a reduction of bone turnover due to anti-resorptive effects of krokodil. C-telopeptide is a predicting factor for the visual identification of necrotic bone margins during surgery.

Microbiological cultures from facial bones in reported patients with osteonecrosis resulted in both autochthonous and allochthonous microorganisms. In the study by Basin,[15] microbiological cultures of 35 patients were examined. In 40% of the reported patients a monoculture was isolated, in 54.2% associations with several microorganisms were found and in 5.7% the culture was sterile. Microorganisms as *Streptococcus salivarius*, *Streptococcus milleri* group, *Enterococcus faecalis, Actinomyces vicosus* and *Candida albicans* were present.[15] The chronicity of the disease, as well as uncontrolled taking antibacterial drugs and antiseptics, contributes to the change of oral microflora and the formation of antibiotic-resistant strains.[15] Open areas of necrotic bone were reported to be resistant to standard pharmacological treatment.[12,13]

The most frequently described onset factor for developing osteonecrosis development of both jaws was tooth extraction by a dentist or the patient him- or herself.[8,10,11,15] The onset of the osteonecrosis occurs within 18 months after tooth extraction. Hakobyan and Poghosyan reported osteonecrosis 18 months after an extraction in the mandible and 12 months after an extraction in the maxilla.[8] Poghosyan *et al.*[11] reported bone exposure immediately after tooth removal or after 1–12 months. Hakobyan *et al.*[10] reported an average of 8 months ± 1.6 (range: 3–12 months). Other trigger factors for onset of osteonecrosis may be a poor quality of removable or fixed dentures, failed endodontic treatment, marginal or apical periodontitis, acute or chronic oral mucosal or bone trauma, anatomical features of the jaws (exostoses, palatal torus) and poor oral hygiene.[11]

Soft tissue

Clinical aspects of the soft tissue in patients using krokodil are often associated with osteonecrosis of the maxillofacial bones. Soft tissue volume is increased in patients with osteonecrosis of the jaw.[6,7,12,13] (Severe) gingival recession with exposed alveolar process of the bone is also frequently reported.[6,7,12,13,14,15] From the empty dental sockets, exposed bone and/or gingival sulcus often a purulent discharge is excreted with an ichorous smell.[9,12,14,15] Defects in the vestibular mucosa over exposed bone in full height have been reported in the study of Hakobyan.[10] The surrounding mucosa is mainly having a pale pink color and is generally not hyperemic.[8,9,11] However, Hakobyan and Poghosyan[8] reported hyperemic areas on the pale pink mucosa. Hakobyan[14] found generalised bleeding on probing in all patients studied while examining the gingiva.

When krokodil is orally administered (drinking or sniffing), redness, irritation and erosion of the mucosa of the oral cavity and pharynx is reported.[2]

Gingivitis and periodontitis

Periodontitis manifested as hyperemia, oedema of the gingiva, bleeding on probing, destruction of interdental septae and tooth mobility in 89.5% of krokodil-using patients in the study of Hakobyan.[14] In six cases there was a resorption of interdental septae up to 1/3 of the original height, in eight cases to 2/3 and in three cases more than 2/3 of the original height of the interdental septae was resorbed. Mobility of the teeth related to krokodil use was also reported by Hakobyan and Poghosyan.[9] Gingivitis was present in 10.5% of the patients in the study of Hakobyan.[14] Just as described above these patients showed hyperemia, edema, bleeding on probing of the gingiva, however, a destruction of interdental septae and teeth mobility were absent.

Changes in the periodontal fissure were radiographically observed by Babkova.[6,7,12,13] In most of the studies a widened periodontal fissure with sclerotic end plates was found in almost half of the patients.[6,7,13] In one third of the patients in the Babkova study[12] an expansion of the periodontal fissure was found. Expansion and sclerosis was present in 19% of the reported patients, while sclerosis without expansion was present in 12% of the investigated patients. In 34% of the subjects, no pronounced changes in the periodontal

gap were revealed and in 2% of the patients there was a narrowing of the periodontal gap. Radiographically massive diffuse periosteal deposits were frequently found, predominantly present in the lower jaw.[6,7,13]

Teeth

In the majority of the included studies, most patients no longer had a full set of teeth.[12] In some cases residual roots of teeth (with or without sclerosis) were present.[12] In multiple studies 100% patients were found to have one or more empty dental sockets.[6,7,8,13] However, Lemon describes a case where all teeth are present.[5] Babkova[12] describes partial secondary edentulousness in his case series of patients and Hakobyan[14] describes fully edentate krokodil users in his study.

The incidence of caries in krokodil users has been investigated by Hakobyan.[14] From this study it was clear that the prevalence (100%) and intensity of caries is very high.[14] Dental plaque or calculus was visually detected in 17 patients, after a methylene blue staining dental plaque was detected in another four patients. The plaque was mainly present in the cervical region of the teeth. In the two edentulous patients, deposits on removable dentures were found.

Caries probably develops asymptomatically in patients using krokodil. Basin[15] investigated 15 patients and reported that the use of synthetic narcotic drugs containing phosphorus compounds had a significant effect on the neuro-receptor in the pulp of intact teeth. The threshold of electro-excitability of the pulp of intact teeth was decreased two to 20 times after krokodil use compared to the normal situation. A pronounced decrease in the threshold for electrostimulation of intact teeth can reduce the pain sensitivity threshold, which subsequently can lead to asymptomatic caries development and complications.

Other reported aspects were a recent discolouration of the teeth, and destroyed crowns.[12]

Oral hygiene and other oral aspects

Reported patients using krokodil have a poor general and oral hygiene.[5,11,12] One study reported that more than half of the patients did not brush their teeth for a year or more.[14] The other patients in this study brushed their teeth once a day, but not regularly. None of the surveyed subjects had received professional oral hygiene for 4 years or more. However, all patients rinsed their mouth with antiseptic solutions and used antibiotics (prescribed by a dentist or on their own initiative) for osteonecrosis of the jaw.[14]

Whether or not krokodil users received dental treatment for their teeth during the period they were using drugs was mainly dependant on their financial situation and mental status.[14]

All patients investigated by Hakobyan *et al.*[10] reported pain in the midface region. In contrast to this study, Babkova and co-workers[12] found absence of severe pain syndrome. Patients complained about exposed intra-oral bone structures with or without purulent discharge, appearance of fistulas, impaired chewing, change of occlusion, face configurations, dermatological lesions on the face and bad odour.[5,12,15]

Fistulas occur at different locations in the face and neck. Single or multiple fistulae have been frequently reported[11] and may appear intra- and/or extra-orally in the area of the nose and orbit or in the submandibular region.[8,12,14] In all patients described by Hakobyan *et al.*[10] purulent discharge from the affected area and nose was present. Other studies showed purulent discharge from both maxillary sinuses.[10] Additionally, during surgery a thickened sinus floor[8] and maxillary sinusitis were observed in a few patients with osteonecrosis of the upper jaw.[6,7]

Treatment

For drug-related osteonecrosis of the jaw, surgical treatment was the main option.[9,11] Surgical treatment includes expanded necrectomies, complete or partial resection of the mandible, maxilla and maxillofacial bones and segmental jaw resection with further implantation.[12] During surgery, resection of necrotic bone beyond 0.5 cm of the visible borders of osteonecrosis towards the healthy tissues was recommended.[9,11] It is necessary to remove the mobile parts of the necrotic bone, all the dead bony tissue up to revealing multiple various-sized blood vessels of the bone.[11] For a successful treatment the patient should refrain from using krokodil in the pre- and postoperative period.[11]

Conservative treatment before surgery recommended by Poghosyan includes detoxification therapy with an isotonic saline solution, a 5% glucose solution or Ringer's solution. In case of necrotic bone suppuration antibacterial and antifungal therapy has to be provided. In addition, it is recommended to treat the patients in a drug addiction clinic and provide them oral hygiene instruction.[11]

Complications during (surgical) treatment

In 23% of cases recurrence of osteonecrosis after surgical treatment of the mandible was reported.[11]

After surgery in the maxilla, oroantral communication was found in 38% of the reported patients.[11] Unilateral or bilateral oroantral communications of different size may emerge, after resection or sequetrectomy in the distal maxilla. Partial and total nasal cavity floor defects, isolated maxillary sinus floor defects and bilateral maxillary sinus floor defects after necrotic bone removal have been reported.[9,10] In the same study, it is described that a spontaneous closure of these defects was possible. A possible complication of treating the defect in patients with maxillary osteonecrosis is the development of a maxillary sinusitis.[6] Also the occurrence of granulation tissue growth in the maxillary sinus has been reported.[10]

Radical surgical interventions in patients with osteonecrosis and the formation of persistent deformities of the middle and lower facial areas could lead to dysfunction in speech, chewing food, and swallowing.[15]

Krokodil users primarily consult a physician or dentist for pain relief. Once the pain is relieved, most of them do not visit the physician or dentist for a postoperative checkup.[10]

Seven clinical studies reported krokodil users infected with hepatitis C, hepatitis B, HIV or tuberculosis (TBC). The most frequent reported infection was hepatitis C in seven studies (92.5–100%). Five studies reported infection of patients with HIV (2.5–15.8%). Two studies reported patients infected with TBC (2.4–6.6%). One study reported infection with hepatitis B among krokodil users: (5%). During dental treatment of (former) krokodil users, the dentist should be aware of the potential presence of these infectious diseases and apply additional infection prevention precautions.

Discussion

The aim of this systematic review was to provide an overview of how krokodil (desomorphine) potentially affects oral health. Osteonecrosis is frequently described in patients using krokodil. The pathogenesis of the osteonecrosis is not completely elucidated, but it is possible that different mechanisms play a role in the development and maintenance of the osteonecrosis of the jaw among krokodil users. The symptoms of krokodil-associated

osteonecrosis are comparable with phosphorus and bisphosphonate-induced necrosis of the jaws. The clinical picture of osteonecrosis in krokodil users is similar to cases of 'phossy jaw' and medication-related osteonecrosis of the jaw (MRONJ). Phosphorus osteomyelitis of the jaws was previously described in factory workers producing matches in the late nineteenth century. These workers developed gingivitis, periodontal disease, alveolar crest bone sequestra, draining fistulae, pathologic mandible fractures and loss of teeth after exposure to phosphorus fumes and phosphorous paste. In medication-related osteonecrosis of the jaw, patients suffer from symptoms as exposed bone, intra- or extraoral fistulas, delayed healing after dental extraction, focal osteosclerosis, tooth mobility, sinusitis and pathological fractures. Similar to osteonecrosis due to the use of krokodil, medication-related osteonecrosis occurs more frequently in the mandible than in the maxilla.[17,18]

The intravenous administration of krokodil provides high concentration of phosphorus in the blood, which cannot all be cleared by the kidneys.[19] Possibly the phosphorus, present as contamination in the krokodil, reacts with substances in the body like CO_2, H_2O and amino acids to produce a potent amino bisphosphonate.[20]

The phosphorus in krokodil penetrates bone tissue, affecting the activity and number of osteoclasts, high concentration of phosphorus in the resorption lacunae will impair cytoskeleton formation by osteoclasts. The secretion of lysosomal enzymes will be reduced, with a subsequent reduction in the resorption capacity of the osteoclast, a less efficient bone resorption and a reduced bone turnover.[20,21] However, not all complications of krokodil are likely to be related to contamination of the drug with red phosphorus. Other diluting agents used during the production of krokodil, such as gasoline and iodine, are associated with serious toxic injury to the lungs and with thyroid dysfunction.[22,23]

Krokodil users have a high prevalence of caries. This is comparable to opiate users in general, who have a greater number of decayed teeth and fewer restored teeth compared to controls,[24] and probably related to diet with a preference for a high concentration of simple sugars. This, in combination with the possible xerostomic effect of opiates, oral neglect, lack of motivation, shortage of money, limited education and difficult access to dental healthcare services,[15,18,25,26] probably explains the high caries prevalence. A decrease in threshold for electrostimuli of intact teeth has been reported in patients using krokodil. This reduced pain sensitivity could lead to asymptomatic development of caries and complications.[15]

Factors contributing to the development of periodontal disease in krokodil users could be a high dental neglect and xerostomia, resulting in an increased accumulation of plaque. Direct effects of opioids on immune function have also been described: a reduction in number of lymphocytes, a reduced CD4:CD8 lymphocyte ratio, reduction in immunoglobulins, production of TNF production and suppression of NK cell activity.[25] The frequent use of antibiotics in patients with osteonecrosis of the jaws made it difficult in some cases to differentiate gingivitis from mild forms of periodontitis.[14]

In addition to the factors mentioned above, several studies reported immunodeficiency, reduced number of erythrocytes, imbalance of pro- and anti-inflammatory cytokines, iron deficiency, increased antigenic activity caused by high content microorganisms in the oral cavity with the use of phosphorus-containing drugs. In addition, the frequently reported (untreated) infections with HIV in krokodil users can have negative effects on the immune system. These factors can also play a role in the development and maintenance of the damage in oral and maxillofacial tissues and could induce an inadequate response to the damaging agents.[15,21]

Dental treatment of patients who use krokodil can be complicated by several factors. These factors are the degree of destruction of the tissue of the jaw bones, pathological fractures, perforated maxillary sinusitis and purulent discharge from soft tissues. Continued use of the drug, the presence of infectious diseases or severe comorbidities and an impaired immunological status will also complicate treatment.[15] Patients who inject drugs have a high risk of cardiac complications like endocarditis or cardiac failure.[3,25] Other systemic effects of the use of krokodil include necrotic ulcerative lesions of the skin, soft tissue infections, liver and kidney inflammation, pneumonia, meningitis, multiple organ failure, and loss of cognitive functions. Therefore, when treating patients using krokodil it is important to be aware of the medical history of the patients. Although some authors recommend antibiotic prophylaxis prior to invasive dental procedures and oral surgery in order to prevent a subsequent exacerbation of endocarditis.[3,25] this suggestion is not supported by the current NICE guidelines.[27] Dental treatment may also be complicated by a reduced response to administered local anesthetics,[25] impaired motor skills, reduced memory and concentration problems of krokodil addicts.[28]

Considering the high analgesic effect of the active substance desomorphine in krokodil, it is difficult to find a good analgesic for patients who have stopped using the drug and are eligible for invasive dental treatment. Opiates should be used with caution for pain relief, as this can lead to a relapse in drug use and drug dependence.[29] Also tolerance for opiate drugs may occur, which can cause a decreased analgesic efficacy of opioid analgesia. However, tolerance to one opioid drug does not necessarily confer tolerance to another.[30] Therefore codeine or other opiate drugs might not be sufficient as a painkiller, and nonsteroidal anti-inflammatory drugs should be used with caution due to possible kidney failure.[19]

However, ketorolac thromine-thiamine (Ketanov), a drug from the group of nonsteroidal anti-inflammatory drugs, can be used intramuscularly. It takes 17 minutes to work and, the period of complete analgesia ranges from 2.5 to 8 hours. Patients reported a high efficacy of anesthesia and a prolonged effect of ketorolac thromine-thiamine compared to other nonsteroidal anti-inflammatory drugs. Complications and side effects of ketorolac-thromine-thiamine were not observed.[29]

Several studies report that the potent analgesic effect of the active substance desomorphine in krokodil could lead to a delay in seeking medical care,[1] and krokodil users seem to seek (dental) treatment only when the disease is at an advanced stage and symptoms have become severe.[15]

Limitations, quality assessment of evidence and bias

The results of this review need to be interpreted with caution. This review was mainly limited to retrospective case series and case reports, which have a low level of evidence. The patient population described in the different studies by Babkova and co-workers may overlap, making it possible that the same patients have been included in several publications from these authors.[6,7,12,13] The included studies showed

a high variation in number of participants and a large heterogeneity in clinical outcome measures. A majority of the included papers (n = 10) reported the use of krokodil drug without information about concomitant use of other drugs. One study reported that the patients also consumed cigarettes and alcohol on a regular base, and used heroin, cannabinoids and/or benzodiazepines before they became addicted to krokodil.[14] Another study from Basin[15] reported that four patients also used the synthetic narcotic drug pervitin. This means that, in some cases, the oral complications described could be as a result of other drugs used.

Since the drug krokodil is most frequently used in Eastern Europe and Russia, most of the studies come from this region. There was no restriction on language when searching electronic databases or reviewing reference lists. However, it is likely that not all of the studies published in Russian were identified for this review. For a subsequent study, electronic databases in languages such as Russian, Armenian and Georgian could also be searched.

Nevertheless, this review provides an important overview of the oral health problems observed in patients who use or have used the drug krokodil.

Conclusion

Osteonecrosis of the maxillofacial bones is a serious and mutilating oral side effect associated with krokodil use, other oral aspects associated with its use include mucosal changes, high risk of caries and periodontitis. In addition, physical effects of the drug, which can indirectly affect oral health, are also described. The use of krokodil drug can interfere with dental and oral- and maxillofacial treatment.

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