POSSIBILITIES OF PAIN MANAGEMENT DURING PHOTODYNAMIC THERAPY

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Abstract

The authors consider the possibilities of pain management during photodynamic therapy (PDT) of visible tumors based on the observation of 102 patients. Of the total number of patients, 62 had verified basal cell skin cancer, 10 people - squamous cell skin cancer, another 10 - oral and oropharynx mucosa cancer, 8 – oral leukoplakia and dysplasia, in 6 - lower lip cancer, in 4 - breast cancer, in 2 - other localizations of neoplasms.
In 15 patients, nonsteroidal anti-inflammatory drugs (NSAID) were used as pain management, in 69 - a combination of NSAID with tramadol, in 14 - nerve block anesthesia, in 4 - PDT was performed under general anesthesia.
The intensity of pain syndrome during laser irradiation of the tumor was assessed on the verbal rating scale (VRS). The absence of pain was recorded in 9% of cases. Mild pain was noted by 58% of patients, moderate pain - 20%, severe pain - 10%, very severe pain was noted by 3% of patients.
The degree of expression of pain syndrome during PDT depends on the incidence of a lesion, histological form of tumor, and method of anesthesia. NSAID alone, or in combination with an opioid analgesic, allows effective control of pain syndrome in PDT of basal cell skin cancer in 89%, in PDT of squamous cell skin cancer in 66% of observations. Nerve block anesthesia allows stoping pain syndrome during PDT of oropharyngeal tumors.

Keywords: photodynamic therapy, pain, anesthesia, skin cancer, oral cancer, oral leukoplakia.
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ВОЗМОЖНОСТИ ОБЕЗБОЛИВАНИЯ ПРИ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ

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Резюме

Авторы рассматривают возможности обезболивания при фотодинамической терапии (ФДТ) опухолей визуальных локализаций на основе анализа данных 102 пациентов. Среди пациентов, включенных в выборку, у 62 верифицирован базальноклеточный рак кожи, у 10 – плоскоклеточный рак кожи, у 10 – рак слизистой оболочки полости рта и ротоглотки, у 8 – лейкоплакия и дисплазия слизистой оболочки полости рта, у 6 – рак нижней губы, у 4 – рак молочной железы, у 2 – новообразования иных локализаций.
У 15 пациентов для обезболивания применяли нестероидные противовоспалительные препараты (НПВС), у 69 – сочетание НПВС со слабыми опиоидами (трамадолом), у 14 – проводниковую анестезию, у 4 ФДТ проводили под общим обезболиванием.
Интенсивность болевого синдрома оценивалась в процессе проведения лазерного облучения опухоли по шкале вербальных оценок (ШВО). Отсутствие болевых ощущений зафиксировано в 9% наблюдений. Слабую боль отмечали в 58% наблюдений, умеренную боль – в 20%, сильную боль – в 10%, очень сильную боль – в 3% наблюдений.
Степень выраженности болевого синдрома при проведении ФДТ зависит от распространенности поражения, гистологической формы опухоли и способа обезболивания. НПВС в самостоятельном варианте или в сочетании с опиоидным анальгетиком позволяют эффективно контролировать болевой синдром при ФДТ базальноклеточного рака кожи в 89%, плоскоклеточного рака кожи – в 66% наблюдений. Проводниковая анестезия позволяет купировать болевой синдром при проведении ФДТ опухолей орофарингеальной области.

Ключевые слова: фотодинамическая терапия, боль, анестезия, рак кожи, рак полости рта, лейкоплакия полости рта.

ORIGINAL ARTICLES

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Introduction

Photodynamic therapy (PT) is a dynamically developing modern method of treatment of malignant neoplasms and a number of pre-tumor diseases and conditions (leukoplakia and dysplasia of the oral mucousa, actinic skin keratosis, vulva kraurosis, etc.) [1]. One of the important practical aspects of the use of tumor PDT in clinical practice is the problem of pain relief. It is not recommended to use local infiltration anesthesia for pain relief during PDT, which is why the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics (tramadol, promedol), sedative medications (Phenosepam, Diphenhydramine, Relanium), are administered parenterally 40–60 minutes before the procedure. When tumors are localized on the skin and mucous membranes, local anesthetics can be used in the form of an ointment (applied on the skin) or by irrigation of the mucous membrane with lidocaine solution [2]. In some cases, PDT is performed with spinal anesthesia or with general anesthesia; cooled air and conduction anesthesia are also used [3].

The intensity of the pain syndrome grows with increasing laser power density and with a large area of exposure [4, 5]. In addition, for a number of photosensitizers such as derivatives of phthalocyanine, M-tetrahydroxophenyl chloride (mTHPC), laser irradiation resulted in a high degree of pain [6]. Insufficient level of analgesia may result in patients' refusal to continue treatment [7].

A significant proportion of patients receiving PDT are elderly and senile. These patients usually have multiple comorbidities that limit the use of NSAIDs and opioid analgesics. Older people are often not prepared to tolerate the minor pain associated with PDT. With tumor localization on the mucous membrane of the oral cavity, oropharynx, lower lip, or genitals, photodynamic reaction causes a high intensity pain.

Materials and methods

Our study included 102 patients treated with PDT. The treatment was performed at the Lipetsk Regional Cancer Center from January 2017 to September 2019. Photosensitizers of the chlorin series were used: Radachlorin (LLC "Rada-PHARMA", Russia, registration certificate No. LS-001868 from 16.12.2011) at a dose of 1.0–1.2 mg/kg of body weight, Photolon (RUE Belmedpreparaty, Republic of Belarus, registration certificate П N015948/01 of November 30, 2012) at the rate of 2.0–2.5 mg/kg of body weight, photoran e6 (OOO "Kompaniya DEKO", Russia, registration certificate No. LP-004885, dated 13.06.2018) at a dose of 2.0–2.5 mg/kg of body weight. The calculated dose of the drug was dissolved in 200 ml of 0.9% sodium chloride solution administered IVFD for 30 minutes. Photosensitizer exposure time was 3 hours. Irradiation was performed with MILON-LAKHTA laser (OOO "Milon Laser", Russia) with a wavelength of 662 nm. The tumors were irradiated with macro- and microlenses.

The study included 102 patients, 62 of them with verified basal cell skin cancer, 10 with squamous cell skin cancer, 10 with cancer of the oral mucosa and oropharynx, 8 with leukoplakia and dysplasia of the oral mucosa, 6 with lower lip cancer, 4 with intradermal metastases of breast cancer, 2 with other localization of the pathological process. In 40% of cases, PDT was performed for recurrent neoplasms. 69% of patients were 70 years old or older at the time of treatment.

The average diameter of the pathological focus was 34 ± 27.8 mm, and the average number of foci per patient was 1.3. In 55% of cases, the diagnosis was verified cytologically, and in 45% histologically. The average number of radiation fields per patient was 2.7, and the average diameter of the radiation field was 27 ± 12.5 mm. The power density of the laser radiation was 469 ± 261 mW/cm^2, and the dose density per field was 258 ± 99.7 J/cm$^{2.}$

The intensity of the pain syndrome was assessed during laser irradiation of the tumor on a verbal rating scale (VRS): 0 – no pain, 1 point – mild, 2 – moderate, 3 – severe, 4 – very severe or unbearable pain (Fig. 1) [8].

Results and discussion

When performing laser irradiation of the tumor during PDT against the background of using one or another method of anesthesia, the absence of pain was recorded in 9% of cases, mild pain was stated by the majority of patients, 58%, moderate pain by 20%, severe pain by 10%, very severe pain by 3% of patients (Fig. 2).

15 patients were administered NSAIDs for analgesia, 69 had a combination of NSAIDs with tramadol, 14 had conduction anesthesia? and 4 had PDT under general anesthesia. Analgesia options in PDT depending on the localization and histological form of the tumor are shown in Fig. 3.

The analyzis of factors that affect the intensity of pain revealed that the least pronounced pain syndrome

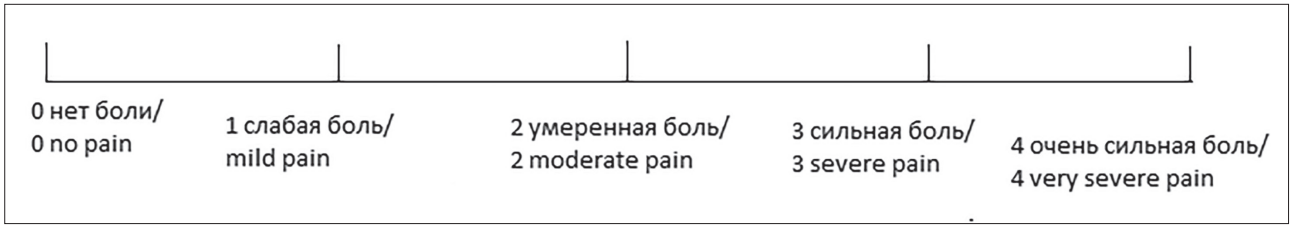

Рис. 1. Шкала вербальных оценок интенсивности болевого синдрома
Fig. 1. A verbal rating scale of pain syndrome intensity

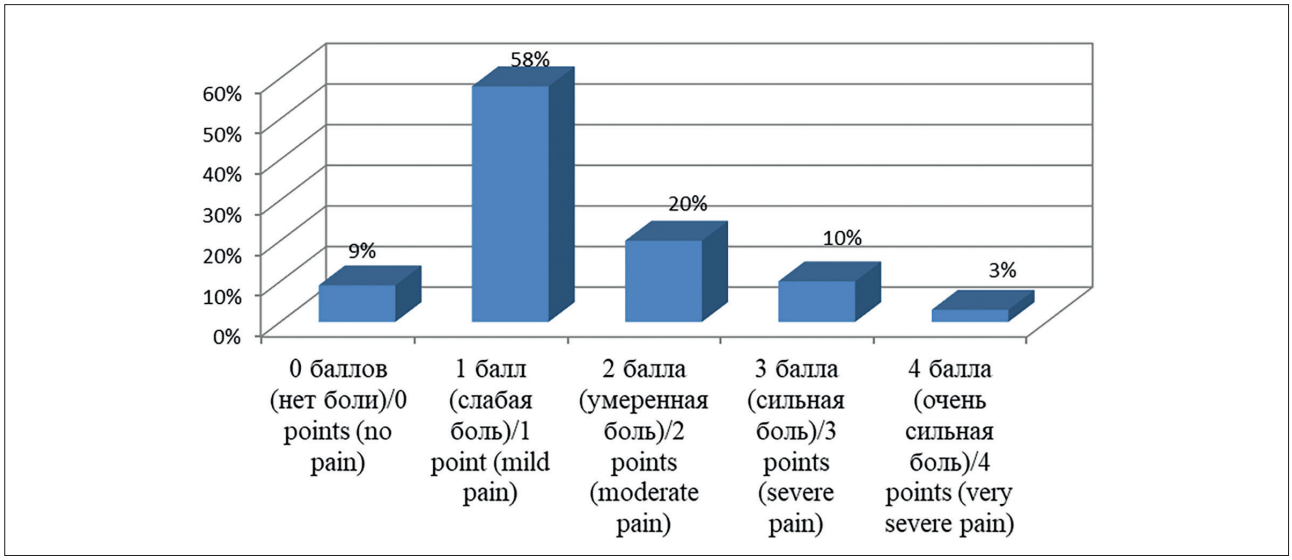

Рис. 2. Интенсивность болевого синдрома по шкале вербальных оценок при проведении фотодинамической терапии (n=102)
Fig. 2. Pain syndrome intensity on the verbal rating scale during photodynamic therapy (n = 102)

(0–1 points) was observed in the treatment of basal cell skin cancer (89%), cancer of the oral and pharyngeal mucosa (100%), lower lip cancer (92%); nevertheless, in the treatment of squamous cell skin cancer, this indicator was 66%, and in PDT of leukoplakia and dysplasia of the oral mucosa, 78% (see Table).

This is due to the fact that in the treatment of patients with cancer of the oral mucosa and pharynx and cancer of the lower lip, we used conductive anesthesia in the majority of cases, which allowed us to achieve good control of the pain syndrome. With leukoplakia of the oral mucosa, a common process is often observed that involves various anatomical departments over a large area, making it difficult to perform conduction anesthesia and causing a relatively high level of pain impulses. A higher level of pain during PDT for squamous cell skin cancer is due to significantly larger lesion size and deep infiltration of the underlying tissues by the tumor compared to those observed in basal cell carcinoma (see Table).

The photosensitizer used did not affect the intensity of the pain syndrome, since in our study all the drugs used were classified as derivatives of e6 chlorin.

Severe pain during PDT leads to longer treatment time, as it is necessary to take breaks between the sessions of laser irradiation of the tumor. In 2 patients with stage II squamous cell carcinoma of the scalp, we were unable to complete the laser irradiation session due to severe pain and the refusal to continue the procedure with tramadol analgesia in combination with NSAIDs.

Despite the lack of recommendations for the use of local infiltration anesthesia in PDT, it was administered to 4 patients whose pain syndrome was not stopped by NSAIDs and opioid analgesics. The patients belonged to the 80+ age category and were treated for malignant neoplasms of the scalp or trunk of grade I–II. As an anesthetic, a 0.2% solution of ropivacaine was used, which was injected into the subcutaneous fat under the tumor, which did not produce a "lemon peel" effect. The pain syndrome was relieved, and the planned dose of laser radiation was administered. Complete tumor resorption was achieved in all 4 patients.

In 14 cases, we used conduction anesthesia for PDT of oropharyngeal tumors, since the treatment of neoplasms of this localization is accompanied by a significant pain

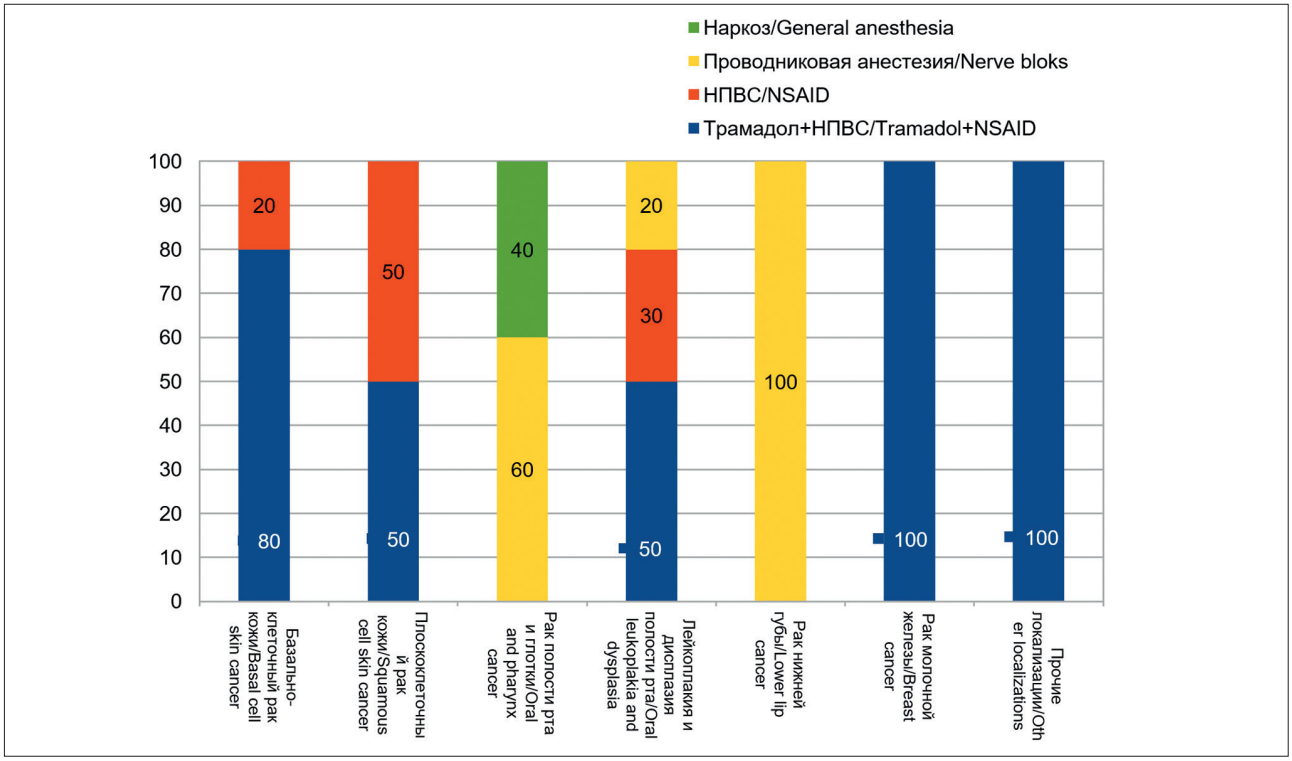

Рис. 3. Соотношение методов обезболивания при ФДТ различных нозологических форм опухолей
Fig. 3. Percentage of anesthesia methods used during PDT of various nosological forms of tumors

syndrome, which cannot be effectively controlled by the systemic administration of analgesics and sedatives. A 0.2% solution of ropivacaine was used as an anesthetic.

Ropivacaine is a long-acting local anesthetic of the amide type. It creates a reversible block of voltage-dependent sodium channels?and, therefore, prevents the generation of impulses in the endings of sensitive nerves and the conduction of impulses along nerve fibers. Conduction anesthesia does not interfere with blood supply and oxygenation of the tumor tissue, which is a necessary condition for the development of a photodynamic reaction. Ropivacaine action continues for at least 4–6 hours, which allows for excluding the period of the most severe pain impulses.

For cancer of the lower lip, mandibular anesthesia was used in combination with mental nerve block. Mandibular anesthesia was performed as follows. By index finger palpation, we determined the anterior edge of the lower jaw branch, inside of which the retromolar fossa was felt, and the temporal ridge behind it, which serves as a reference point for the needle injection site (Fig. 4). The injector was placed at the level of the premolars of the opposite side, the needle was inserted inside from the temporal ridge at a distance of 0.5–1 cm above the masticatory surface of the lower molars, directing the needle from the 2nd premolar of the opposite side outward and posteriorly until the contact with the bone. Immediately after the puncture, 0.5 ml of anesthetic was administered to anesthetize the lingual nerve. After the needle was pushed deeper by 2 more cm and reached the bone groove, the remaining part of the anesthetic solution was injected to block the lower alveolar nerve [9, 10]. Mandibular anesthesia zone: the mucosa of the alveolar process of the lower jaw from molars to pre-molars of the corresponding side, the anterior 2/3 of the lateral surface of the tongue and half of the lower lip.

To perform mental anesthesia, the needle was inserted into the mucobuccal fold of the lower lip between the 2nd premolar and the 1st molar, and the needle was moved 1–2 cm to contact the bone, and the anesthetic was injected. Anesthesia zone: the frontal part of the soft tissues of the lower lip half, the mucous membrane of the mouth vestibule from the 2nd premolar to the 1st incisor of the opposite side, the mucous membrane of the alveolar process on the side of anesthesia.

For analgesia of the cheek mucosa, in addition to mandibular anesthesia, buccal nerve anesthesia or torus anesthesia was performed, and with the tumor localized in the upper posterior parts of the oral cavity (the posterior parts of the alveolar process of the upper jaw, the mucosa of the transitional fold and the upper posterior part of the cheek mucosa), tuberal anesthesia was performed.

Таблица
Исходные данные пациентов с отсутствием и слабой выраженностью болевого синдрома при фотодинамической терапии
Table
Initial data for patients with absent or mild pain syndrome during photodynamic therapy

Нозологическая форма Nosological form	Возраст (лет)* Age (years)*	Среднее число полей облучения (абс. ч.) Average number of irradiated areas	Средний размер очага (мм) Average focus size (mm)	Плотность дозы (Дж/см^2)* Dose density (J/cm^2)*	Плотность мощности (мВт/см^2)* Power density (mW/cm^2)*	Доля пациентов с оценкой болевого синдрома 0–1 балл (%) The proportion of patients with a pain score of 0–1 points
Базальноклеточный рак кожи (n=62) Basal cell skin cancer (n = 62)	74,5/78	2,6	23,8	293/300	524/509	89
Плоскоклеточный рак кожи (n=10) Squamous cell skin cancer (n = 10)	76,7/79	4,5	91,6	356/350	280/194	66
Рак слизистой оболочки полости рта и глотки (n=10) Oral and oropharynx mucosa cancer (n = 10)	61,3/64,5	3,0	22,5	282/290	401/380	100
Рак нижней губы (n=6) Lower lip cancer (n=6)	76,1/79,4	2,7	20,7	280/300	477/440	92
Лейкоплакия и дисплазия слизистой оболочки полости рта (n=8) Oral leukoplakia and dysplasia (n=8)	64,8/67	5,4	17,5	108/70	528/477	78

Примечание: * – среднее значение/медиана
Note: * – average value/median

Buccal nerve anesthesia was performed as follows. The needle was injected into the area of the anterior edge of the coronal process at the level of the masticatory surface of the upper molars into the cheek mucosa, directing the syringe from the opposite side. The needle was moved 1.0–1.5 cm to the anterior edge of the coronal process, and 1–2 ml of anesthetic was injected. Pain relief zone: the mucous membrane and the skin of the cheek.

When conducting torus anesthesia, anesthetic solution was injected into the region of the mandibular torus. It is located at the junction of the bony ridges coming from the coronoid and condylar processes, above and anteriorly from the bony growth of the lower jaw. The lower alveolar, lingual and buccal nerves are located below and inside the torus, surrounded by loose cellular tissue. When an anesthetic is administered to this area, these nerves can be blocked simultaneously. The syringe is placed on the molars of the opposite side. The needle is inserted into the groove formed by the lateral slope of the pterygomandibular fold and the cheek, at a distance of 0.5 cm below the masticatory surface of the upper 3rd molar (Fig. 5) [9, 10]. The needle is pushed 0.25–2 cm to the bone and 1.5–2 ml of anesthetic is injected (blocking the lower alveolar and buccal nerves). Move the needle a few millimeters in the opposite direction and inject 0.5–1.0 ml of anesthetic (blocking the lingual nerve). Area of anesthesia: all the teeth of the corresponding side, the bone tissue of the alveolar process of the lower jaw, the gum from the vestibular and lingual sides, the mucous membrane of the hyoid region, the front 2/3 of tongue, the skin and mucosa of the lower lip, the skin of the chin of the corresponding side, the mucosa and skin of the cheek.

Posterior superior alveolar nerve block was performed as follows: with the mouth half open, the cheek is drawn outwards with a spatula or dental mirror. The needle is placed at an angle of 45° to the crest of the alveolar

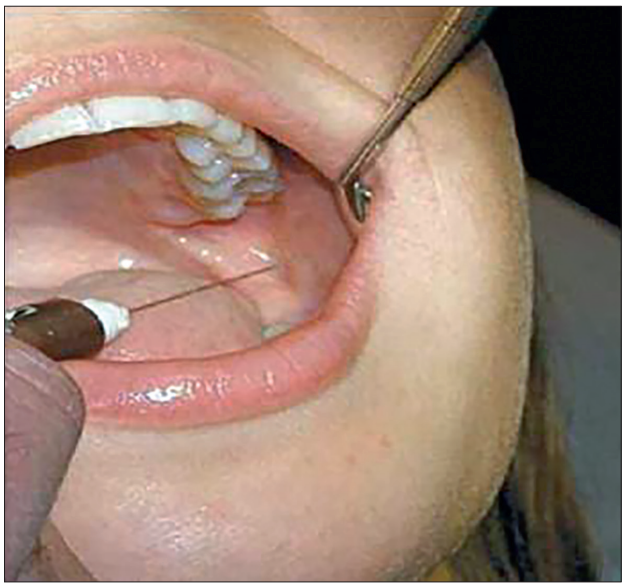

Рис. 4. Выполнение мандибулярной анестезии
Fig. 4. Mandibular anesthesia procedure

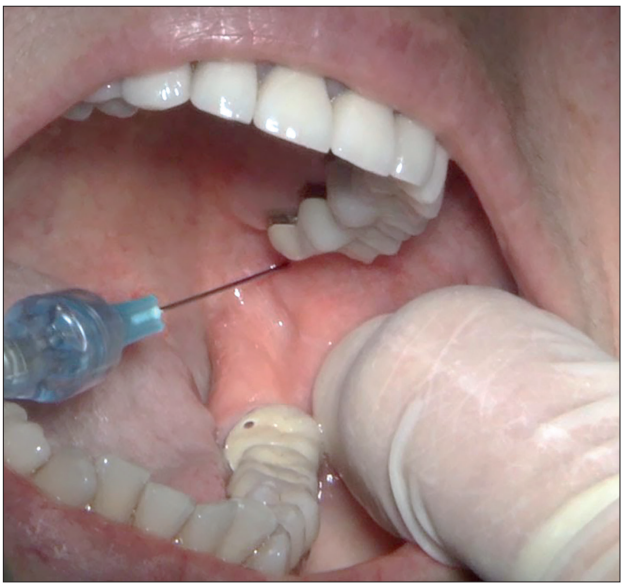

Рис. 5. Выполнение торусальной анестезии
Fig. 5. Torusal anesthesia procedure

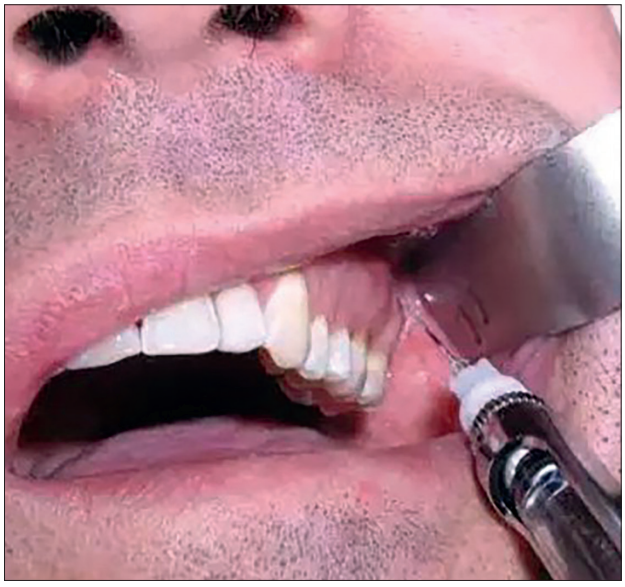

Рис. 6. Выполнение туберальной анестезии
Fig. 6. Tuberal anesthesia procedure

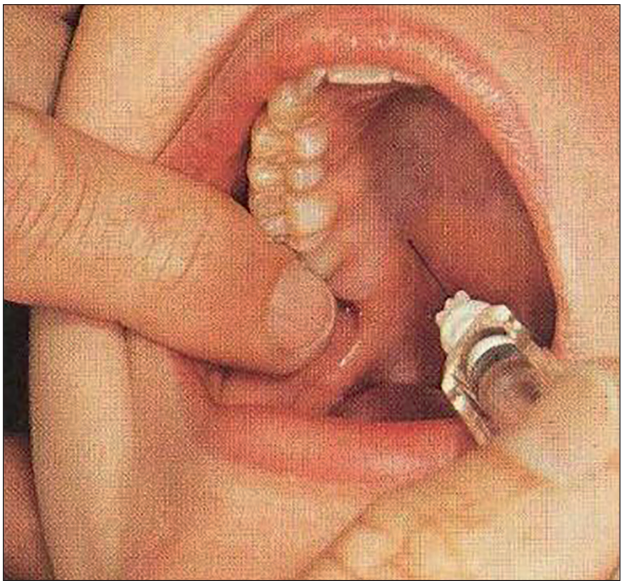

Рис. 7. Выполнение палатинальной анестезии
Fig. 7. Palatine anesthesia procedure

process, its bevel facing the bone. The needle is inserted at the level of the crown of the second molar or between the second and third molars into the mucous membrane, 0.5 cm outwards off from the mucobuccal fold (Fig. 6) [9, 10]. The needle is moved up, back and inwards to a depth of 2.5 cm, with the syringe directed outward so that the needle is always located as close to the bone as possible. To a certain extent, this prevents damage to the arteries, veins of the pterygoid venous plexus and hemorrhage into the surrounding tissues. After administration of 2 ml of analgesic solution, anesthesia is achieved in 7–10 minutes.

In the absence of large molars, the zygoalveolar ridge that runs from the zygomatic process of the upper jaw to the outer surface of the alveolar process located at the level of the first molar is used as a benchmark. The needle is inserted behind the zygo-alveolar ridge, which corresponds to the middle of the crown of the missing second molar. The pain relief zone includes the periosteum of the alveolar process of the upper jaw and the mucous

membrane covering it in the area of these teeth on the side adjacent to the cheek; the mucous membrane and bone tissue of the posterior exterior wall of the maxillary sinus. The posterior border of the pain relief zone is constant. The anterior border may run along the middle of the crown of the first large molar or reach the middle of the first small molar.

For tumors of the anterior parts of the oral floor, mandibular anesthesia was performed on both sides with additional blocking of the lingual nerve in the area of the alveololingual groove. Lingual nerve anesthesia is administered as follows. With a spatula, the tongue is moved in the opposite direction and a needle is inserted into the mucous membrane of the maxillofacial groove at the level of the middle of the crown of the lower 3rd molar, where the nerve lies very superficially. 2 ml of anesthetic is administered. The analgesia zone: mucous membrane of the infrahyoid lobe, the anterior 2/3 of the tongue.

In the cases of tumor localization in the soft palate, palatinal anesthesia was performed. With this anesthesia, the greater palatine nerve is blocked in the area of the greater palatine foramen. For this purpose, the anesthetic must be injected into the area of the greater palatine foramen. It is located at the level of the middle of the 3rd molar crown, in the absence of the latter, posteriorly and internally from the 2nd molar, or 0.5 cm anteriorly from the border of the hard and soft palate. To determine the projection of the greater palatine foramen on the mucous membrane of the hard palate, it is necessary to draw two intersecting lines: one parallel to the border of the hard and soft palate at the level of the mid-crowns of the 3rd molars from the gingival margin to the midline of the upper jaw of the respective side (note that the maxilla is a paired bone), and the other through the middle of the first line and perpendicular to it (from front to back). The intersection point of these two lines will correspond to the projection of the greater palatine foramen.

The method of palatinal anesthesia is as follows. With the patient's mouth wide open, the needle is injected at a distance of 1 cm in front and inside of the projection of the palatine foramen on the mucous membrane, i. e., retreating to the midline (Fig. 7). The needle is pushed up, slightly posteriorly and outwards until it comes into contact with the bone. 0.5 ml of anesthetic is administered. Anesthesia is achieved after 3 to 5 minutes. Palatine anesthesia zone: the mucous membrane of the hard and soft palate, the alveolar process of the upper jaw on the palatine side from the 3rd molar to the middle of the canine crown [9, 10].

The pain syndrome among the group of patients with conduction anesthesia varied from 0 to 1 point; the planned dose of laser radiation was admiinistered in full to all patients.

The indications for the use of anesthesia for PDT included recurrent tumors of the oral cavity and oropharynx in the presence of trismus of the masticatory muscles, postoperative scar deformation of the irradiation zone and difficult-to-reach anatomical localizations of the pathological process.

Conclusion

The severity of the pain syndrome during PDT depends on the histological form of the tumor, the extent of the lesion, and the method of anesthesia. The most pronounced pain syndrome is observed during PDT of squamous cell skin cancer, leukoplakia and dysplasia of the oral mucosa. NSAIDs alone or in combination with an opioid analgesic can effectively control pain in PDT of basal cell skin cancer in 89% of cases, and in PDT of squamous cell skin cancer in 66%. Conduction anesthesia allows you to relieve the pain syndrome during PDT of oropharyngeal tumors. Analgesia for PDT of visual localization tumors in elderly patients should be carried out with due consideration of the localization and prevalence of the pathological process, as well as concomitant pathology and the level of homeostasis compensation.

It is necessary to continue the development efforts aimed at solving the problem of pain relief during PDT. In order to unify approaches to choosing optimal methods of pain management in PDT, it is necessary to integrate the work of clinicians from different centers of the country and conduct randomized trials.

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