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CLINICAL CASE REPORTS

THE USE OF TRANSDERMAL THERAPEUTIC SYSTEMS FOR CHEMICAL PLEURODESIS IN A PATIENT WITH PROLONGED AIR LEAKAGE AFTER LUNG RESECTION FOR CANCER

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ABSTRACT

This clinical observation demonstrates a method of a motivated use of a transdermal therapeutic system (TTS) based on fentanyl for chemical pleurodesis in a patient with prolonged air leakage after lung resection for cancer. The most common complication after elective lung resections is an alveolar-pleural fistula or prolonged air leakage. This clinical phenomenon occurs as a result of communication between the alveoli of the lung parenchyma distal to the segmental bronchus and the pleural cavity. In most cases, air leakage through the drains is eliminated spontaneously, but the frequency of prolonged pneumostasis absence in the postoperative period can reach 25 %, which has a negative effect on the outcomes of surgical interventions due to the development of pneumonia and empyema. Long-term drainage of the pleural cavity does not always end with aerostasis and requires repeated invasive interventions. One of the ways to achieve the tightness of the lung tissue involves various methods of chemical pleurodesis, which is a surgical manipulation – the introduction of a sclerosing chemical substance into the pleural cavity by spraying medical talc through a trocar or a injecting tetracycline solution into the pleural drains. The chemical causes aseptic inflammation and adhesions between the visceral and parietal pleura, followed by obliteration of the pleural cavity. The sclerosant introduction is accompanied by severe pain that can provoke respiratory and/or hemodynamic deficits, up to apnea and life-threatening heart rhythm disturbances. Pain relief during chemical pleurodesis is obviously an important factor in the prevention of a number of complications in patients undergoing surgery for lung cancer. Bolus intravenous injections of narcotic analgesics lead to an analgesic effect, but a short-term one due to the absence of a depot in the body and a sharp drop in the drug concentration in the blood serum. Unfortunately, this method of introducing narcotic drugs can cause various complications in weakened and elderly cancer patients, such as respiratory depression and cardiac arrest. The TTS action is characterized with continuous dosing and the creation of a constant concentration of the narcotic drug over a certain period of time. This method provides a multilevel and systematic approach to pain relief, reduces toxicity and minimizes the inhibition of the central mechanisms of external respiration regulation without causing respiratory and cardiac disorders in patients who underwent lung resection.

Keywords:
lung cancer, lung resection, bronchopleural complications, chemical pleurodesis, anesthesia, transdermal therapeutic systems

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

ПРИМЕНЕНИЕ ТРАНСДЕРМАЛЬНЫХ ТЕРАПЕВТИЧЕСКИХ СИСТЕМ ПРИ ПРОВЕДЕНИИ ХИМИЧЕСКОГО ПЛЕВРОДЕЗА У ПАЦИЕНТА С ДЛИТЕЛЬНОЙ УТЕЧКОЙ ВОЗДУХА ПОСЛЕ РЕЗЕКЦИИ ЛЁГКОГО ПО ПОВОДУ РАКА

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РЕЗЮМЕ

Данное клиническое наблюдение демонстрирует способ мотивированного применения трансдермальной терапевтической системы (ТТС) на основе фентанила при проведении химического плевродеза у пациента с длительной утечкой воздуха после резекции лёгкого по поводу рака. Наиболее распространенным осложнением после плановых резекций лёгкого является формирование альвеолярно-плеврального свища или длительная утечка воздуха. Это клиническое проявление возникает в результате сообщения между альвеолами паренхимы лёгкого дистальнее сегментарного бронха с плевральной полостью. В большинстве случаев утечка воздуха по дренажам устраняется спонтанно, однако частота длительного отсутствия пневмостаза в послеоперационном периоде может достигать 25 % случаев, что оказывает отрицательное влияние на исходы оперативных вмешательств из-за развития пневмонии и эмпиемы. Длительное дренирование плевральной полости не всегда заканчивается аэростазом и требует повторных инвазивных вмешательств. Одним из способов достижения герметичности ткани лёгкого является применение различных методик химического плевродеза, который представляет собой хирургическую манипуляцию – введение склерозирующего химического вещества в плевральную полость путем распыления медицинского талька через троакар или раствора тетрациклина, вводимого в плевральные дренажи. Химическое вещество приводит к асептическому воспалению и образованию сращений между висцеральным и париетальным листками плевры с последующей облитерацией плевральной полости. Введение склерозанта сопровождается сильными болями, способными спровоцировать респираторный и/или гемодинамический дефицит, вплоть до апноэ и жизнеугожающего нарушения сердечного ритма. Очевидно, что купирование боли при проведении химического плевродеза является важным фактором профилактики ряда осложнений у пациентов перенесших хирургическое вмешательство по поводу рака лёгкого (РЛ). Использование болюсного внутривенного введения наркотических анальгетиков приводит к обезболивающему эффекту, но кратковременного характера, что обусловлено отсутствием депо в организме и резким спадом концентрации препарата в сыворотке крови. К сожалению, у ослабленных и пожилых онкологических больных данный способ введения наркотических препаратов может вызвать различные осложнения такие, как угнетение дыхания и сердечной деятельности. Особенностью действия ТТС является обеспечение непрерывного дозирования и создания постоянной концентрации наркотического препарата на протяжении определенного промежутка времени. Данный способ обеспечивает многоуровневый и системный подход к устранению боли, способствует снижению токсичности и минимизирует угнетение центральных механизмов регуляции внешнего дыхания, не вызывая респираторные и кардиальные нарушения у больных, перенесших резекции легкого.

Ключевые слова:
рак лёгкого, резекции лёгкого, бронхоплевральные осложнения, химический плевродез, обезболивание, трансдермальные терапевтические системы

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RELEVANCE

Statistics from the International Agency for Research on Cancer determine the leading place of lung cancer (LC) among other malignant tumors. In the structure of oncological morbidity of the Russian Federation among the male population, tumors of the trachea, bronchi and lung account for 16.9 % [1].

Advances in cancer biology and significant progress in the identification of biomarkers with predictive value for various types of drug therapy allow us to hope for an increase in the effectiveness of RL treatment [2]. Of course, the modern capabilities of the multimodal approach are important, but the surgical method remains the main one in the treatment of patients with LC [3].

The improvement of the technique of radical surgical interventions in patients with RL and the latest technologies of intraoperative prevention of complications still do not completely solve the problems of the complicated course of the postoperative period, and bronchopleural surgical complications often develop after lung resection. The most common complication after planned lung resections is the formation of an alveolar-pleural fistula or prolonged air leakage [4]. This clinical manifestation occurs as a result of communication between the alveoli of the lung parenchyma distal to the segmental bronchus with the pleural cavity [5]. The Society of Thoracic Surgeons of the USA defines prolonged air discharge as an air leak that persists for more than 5 days after surgery. Air discharge after lung resection is observed in 25–50 % on the 1st day after surgery and above 20 % on the 2nd-4th day of the postoperative period [6]. Despite the fact that in most cases air leakage through drains is eliminated spontaneously, the frequency of prolonged absence of pneumostasis after lung resection for cancer according to the literature in the last decade is from 10 to 25 % [7]. In addition, in some patients, air leakage occurs delayed, i.e. 5 or more days after surgery against the background of a seemingly uncomplicated course of the postoperative period.

Prolonged air discharge negatively affects the outcomes of surgical interventions due to the development of complications such as pneumonia and empyema. The frequency of empyema with prolonged air leakage lasting more than 7 days is 10.4 % compared to 1 % with air discharge lasting less than 7 days (p = 0.01) [8]. Prolonged air discharge requires prolonged drainage of the pleural cavity, increasing postoperative pain; violation of lung expansion leads to an increased risk of pneumonia and thromboembolic complications due to reduced mobility of patients [4]. As a result, prolonged air discharge is associated with an increase in hospital mortality [9]. Patients with air leakage have a 3.4 times greater risk of dying than patients without this complication. Patients with prolonged air leakage stay in the hospital much longer, increasing the amount of costs by 30 %. In addition, prolonged air leakage causes a twofold increase in repeated hospitalizations of patients who have undergone lobectomy [10].

Prolonged drainage of the pleural cavity does not always end with aerostasis, which requires repeated interventions of varying degrees of invasiveness to eliminate air leakage [11]. The most effective ways to achieve tightness of lung tissue include various methods of chemical pleurodesis, endobronchial valves, repeated surgical interventions [11; 12]. Repeated surgery with the use of general anesthesia with separate bronchial intubation is accompanied by a significant functional load on the body, increasing the risk of surgical intervention in the group of older patients, as well as in patients with severe concomitant pathology [13].

Chemical pleurodesis is the introduction of a sclerosing chemical into the pleural cavity by spraying medical talc (magnesium hydrosilicate) through a trocar or tetracycline solution injected into drains. The chemical substance leads to aseptic inflammation and the formation of adhesions between the visceral and parietal pleural leaves, followed by obliteration of the pleural cavity [14]. Intrapleural administration of sclerosing drugs is accompanied by a painful reaction up to the development of pleuropulmonary shock with the possibility of its relief only with opioid analgesics [15]. Bolus intravenous administration of narcotic analgesics leads to an analgesic effect, but of a short-term nature, due to the absence of depots in the body and a sharp decrease in the concentration of the drug in the blood serum. Unfortunately, in weakened and elderly cancer patients, this method of administering narcotic drugs can cause life-threatening conditions, such as respiratory depression and cardiac activity with loss of consciousness. At the same time, the lack of adequate anesthesia can provoke apnea, bronchospasm, and collapse of lung areas with acute cardiovascular events [15]. It is obvious that pain relief during pleurodesis is an important

factor in the prevention of a number of complications in patients who have undergone surgery for RL.

To reduce pain symptoms during chemical pleurodesis, we selected a method of anesthesia using a transdermal therapeutic system (TTS) based on fentanyl. The motivation was the peculiarities of using an alternative and non-invasive route of administration of drugs, including opioid analgesics. The peculiarity of the action of TTS is to ensure continuous dosing and the creation of a constant concentration of analgesic drug for a certain period of time.

The purpose of the study: was to demonstrate a case of motivated use of a fentanyl-based transdermal therapeutic system when performing chemical pleurodesis after lung resection for cancer.

CLINICAL CASE

Patient K., 59 years old, was hospitalized at FSBI "Rostov Research Oncological Institute" of the Ministry of Health of the Russian Federation (since 2020 National Medical Research Centre for Oncology of the Ministry of Health of Russia) for specialized antitumor treatment. The main complaints at admission: dull chest pain of a permanent nature, periodic temperature rises. The diagnosis was made at the place of residence: Peripheral cancer of the left lung. Upon further examination, according to the SCT of the chest organs, a peripheral tumor of the upper lobe of the left lung was diagnosed 4.5 × 5.0 cm with germination into the mediastinal pleura, with an increase in the thoracic, bronchopulmonary and lymph nodes of the aortic window up to 1.0 cm. Fibrobronchoscopy: pathology of the tracheobronchial tree was not revealed, there are no signs of tumor centralization. Ultrasound of abdominal organs: hepatomegaly, fatty hepatosis, diffuse changes of the pancreas. The function of external respiration: the vital capacity of the lungs is 45 %, the forced vital capacity of the lungs is 34 %, the volume of forced air when exhaling in 1 second is 37 %, i.e. there is a pronounced decrease in all indicators. Electrocardiography: heart rate 88 beats/min, left anterior hemiblock – distal form, reduction of myocardial repair processes in the anterior-septum region of the left ventricle. Therapist's consultation: hypertension art. 2, arterial hypertension 3, risk 2, chronic heart failure 2 art., chronic obstructive pulmonary disease stage 1, grade 3 respiratory failure 2 art., obesity 2 art. Consultation of a vascular surgeon: varicothrombophlebitis of the right lower limb, chronic venous insufficiency 2 art., functional class 4. Morphological verification obtained as a result of transthoracic puncture: fragments of squamous cell carcinoma.

Based on the examination data, a clinical diagnosis was established: (C34.1) Cancer of the upper lobe of the left lung peripheral form sT2bNxM0 stage II, clinical group 2, Chronic obstructive pulmonary disease stage 1, grade 3 respiratory failure stage 2, hypertension stage 2, arterial hypertension 3, risk 2, chronic heart failure stage 2, Varicothrombophlebitis of the right lower limb, chronic venous insufficiency stage 2, functional class 4. Obesity 2st. Taking into account the clinical stage of RL, the consultation of doctors of the cancer center recommended performing surgical intervention in the volume of an extended upper lobectomy on the left. After preliminary drug preparation, the patient underwent surgery: An extended upper lobectomy on the left, combined with resection of the diaphragmatic nerve and mediastinal pleura. Postoperative therapy was aimed at antibiotic prophylaxis and prevention of thrombogenic complications with relief of postoperative pain by reduced double intramuscular administration of narcotic analgesics against the background of epidural analgesia. The postoperative period up to the ninth day proceeded without complications, when symptoms of pneumothorax appeared after a cough attack. Within three days, clinical and radiological symptoms of pneumothorax increased, and therefore surgeons decided to perform chemical pleurodesis using doxycycline, a semi-synthetic tetracycline – a broad-spectrum antibiotic with bacteriostatic action. As is known, doxycycline has a low resorptive ability and a pronounced adhesive effect [15].

Chemical pleurodesis was performed in the intensive care unit, which is justified by the unpredictable response of the patient's body to the introduction of an aggressive component of therapy. In some cases, during this manipulation, patients had a painful reaction with a collaptoid component in the form of loss of consciousness, respiratory and hemodynamic deficiency, up to apnea and life-threatening cardiac arrhythmia. As a rule, to prevent a painful reaction to the introduction of doxycycline solution into the pleural cavity, 2 ml of 2 % promedol solution was intramuscularly prescribed to the patient 30 minutes before the manipulation, and 1 % morphine solution – 1 ml was injected intravenously immediately before the procedure. Nevertheless, with such a scheme of

anesthesia, acute pain of varying degrees of intensity with the introduction of doxycycline was recorded in each patient, which required additional intravenous administration of narcotic drugs to relieve pain, often without the expected effect. At the same time, the patient's condition was aggravated by the development of poorly predictable manifestations of the toxic effects of opioids, namely, impaired consciousness, breathing, nausea and vomiting. As an alternative analgesia during chemical pleurodesis with doxycycline in patients with prolonged air leakage after lung resections for cancer, NMRC Oncology has proposed and patented a "Method of analgesia using a transdermal therapeutic system" (RF Patent No. 2712918). In clinical practice, the main indication for the use of fentanyl-based TTS is chronic pain syndrome in oncological diseases. When prescribing TTS to patients, the concentration of fentanyl in the applied method of pain relief should be taken into account. So, in the composition of the drug Fendivia®, the content of fentanyl varies in the range from 12.5 mcg/h to 100 mcg/h (1.38–11 mg).

Informed consent of the patient was obtained for anesthesia and processing of personal data. A day before the pleurodesis, a fentanyl-based patch was applied to the patient's shoulder at a dose of 75 mcg/hour. During the day, the patient's subjective well-being, objective respiratory and hemodynamic parameters were recorded, which, when using TTS, remained stable and corresponded to age-related physiological norms. An hour before the chemical pleurodesis, the blood gas composition was evaluated taking into account the following indicators: saturation ($SatO_2$) 93 %; partial voltage of carbon dioxide of arterial blood (pCO_2) 46 mmHg; partial voltage of oxygen of arterial blood (pO_2) 89 mmHg; pH 7.38; deficiency or excess of bases (BE) 2.8; bicarbonate (HCO_{3-}) 22.6 mmol/L. To determine the intensity of pain, a visual analog scale (VAS) was used; before manipulation, the subjective pain score was 0 points. 24 hours after the application of TTS, chemical pleurodesis was performed with doxycycline at a dosage of 500 mg dissolved in 20 ml of saline solution. The chemical pleurodesis was carried out by introducing the drug into the pleural drainage in compliance with the standards of asepsis and antiseptics in the patient's sitting position on the dressing table. During the manipulation, cardiomonitoring recorded the correct sinus rhythm; respiratory function without obvious signs of deficiency (respiratory rate 18 per minute, with pulse oximetry indicators $SatO_2$–94 %, without oxygen insufflation); pain symptoms were absent, subjective assessment of pain intensity by VAS – 1 point. Drowsiness, dizziness, nausea and vomiting characteristic of intramuscular or intravenous administration of narcotic drugs were absent. An hour after pleurodesis, the patient was active, with adequate breathing and stable hemodynamics, he did not complain of pain. Indicators of blood gas composition: $SatO_2$–94 %; partial voltage of arterial carbon dioxide (pCO_2) – 47 mmHg; partial voltage of arterial blood oxygen (pCO_2) – 99 mmHg; pH – 7.36; deficiency or excess of bases (VE) – 3.2; bicarbonate (HCO_{3-}) – 23.8 mmol/dL. The evaluation of laboratory parameters in dynamics demonstrates the stability of the gas composition of the patient's blood.

DISCUSSION

Most alveolar-pleural fistulas in the presence of drainage in the pleural cavity are eliminated spontaneously, and only in some cases prolonged air leakage requires special treatment. Despite the difference in approaches to the management of pleural drains, many surgeons prefer active aspiration of air from a Bobrov jar with a water level of about 20 cm until the morning of the 1st day of the postoperative period with the transition to a water gate, with which a small air leak is effectively controlled. However, with the appearance of subcutaneous emphysema or an increase in pneumothorax, especially a few days after surgery, you should return to active aspiration.

With the advent of portable pleural drainage systems, outpatient treatment of prolonged air discharge has become possible and widespread, provided adequate apposition of the visceral and parietal pleura is achieved. However, such tactics should be carefully weighed, taking into account the latest data on the need for re-hospitalization of 25 % of patients discharged with drainage systems after lung resection, who developed pleural empyema in almost 17 % of cases, which required lung decortication in 12 % of cases [16].

There is an obvious need to use more active methods of treating long-term air discharge, such as chemical pleurodesis with tetracycline, talc, iodine or silver nitrate, the introduction of a blood patch and endobronchial placement of a 1-way valve, which have shown high efficiency. Thus, with chemical pleurodesis, the frequency of resolution of prolonged

air leakage exceeds 95 %, with the installation of an endobronchial valve reaches 93 %, with the use of autoblood patches is 92 % [17].

Chemical pleurodesis by spraying talc is performed under general anesthesia, intrapleural administration of tetracycline or silver nitrate is accompanied by severe pain that can increase respiratory failure and cause cardiac arrhythmia [11]. In other words, chemical pleurodesis, despite its low invasiveness, is a very aggressive surgical manipulation against the patient, requiring adequate anesthetic measures to prevent the development of life-threatening pleuropulmonary shock.

When considering the pathological processes occurring in the body of patients after lung resection for cancer, it is necessary to take into account several factors: significant functional changes in gas exchange due to respiratory insufficiency and hypoxia and an imbalance of tissue and cellular oxidation with a violation of the effective biochemical maintenance of the body [18].

The subjective opinion of the patient in assessing the severity of pain (indicators of the visual-analog scale) and the analysis of laboratory parameters of the blood gas composition during chemical pleurodesis did not have negative dynamics, which may indicate adequate anesthesia and the absence of a stress reaction to aggressive surgical manipulation. On the contrary, in the absence of adequate anesthesia, the patient tries to neutralize pain by reducing the frequency of breathing, the depth of inspiration, suppressing coughing and, as a result, alveolar ventilation decreases with the phenomena of hypoxia and hypercapnia [12; 17]. The absence of changes in the parameters of the blood gas composition clearly demonstrates the stability of the functional state of the respiratory system, which is due to the effectiveness of the therapeutic measure.

The demonstration of clinical observation showed a number of advantages of the method of preventing the development of acute pain during chemical pleurodesis to eliminate prolonged air discharge after lung resection using fentanyl-based TTS. This method provides a multi-level and systematic approach to pain management, helps to reduce toxicity and minimizes the suppression of the central mechanisms of regulation of external respiration, without causing respiratory and cardiac disorders in patients who have undergone lung resection. A gradual increase in the concentration of fentanyl reaches its maximum value 24 hours after the application of TTS with the preservation of the analgesic effect for three days (Instructions for medical use of the drug Fendivia®). The absence of the need for additional anesthesia during and after chemical pleurodesis creates a positive psycho-emotional mood, contributing to a successful recovery. In addition, the advantage of the method is ease of use and cost-effectiveness – a single application of TTS provides sufficient analgesic effect.

The tactics of adequate anesthesia and leveling of the pain symptoms that have arisen, when providing high-tech medical care, must meet modern requirements for acute pain relief with minimal toxic effect, maximum safety of use, contributing to the normalization of the functional state of the patient's body in the early postoperative period. At FSBI National Medical Research Center of Oncology, a method for preventing acute pain during chemical pleurodesis in the early postoperative period due to prolonged leakage and/or persistent hydrothorax after lung resections for LC using a transdermal therapeutic system based on fentanyl has been introduced into everyday clinical practice.

CONCLUSION

Thus, the use of a transdermal therapeutic system for the purpose of relieving acute pain during chemical pleurodesis provides an adequate analgesic effect and prevents the development of cardiorespiratory and toxic complications. This method undoubtedly takes place in the treatment of pain syndrome in LC patients after radical surgical treatment.

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Natalia N. P. – direct conduction of the study;
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