Реферати

ЛЕЧЕНИЕ НЕОСЛОЖНЕННОГО КАРИЕСА ПОСТОЯННЫХ ЗУБОВ У ДЕТЕЙ ШКОЛЬНОГО ВОЗРАСТА В УСЛОВИЯХ ОБЩЕГО ОБЕЗБОЛИВАНИЯ

Коваль О.И.

Цель нашого исследования − обосновать обьем и последовательность выполнения стоматологических манипуляций для лечения неосложненного кариеса постоянных зубов у детей школьного возраста в условиях общего обезболивания. Нами проведен сравнительный анализ результатов лечения неосложненного кариеса постоянных зубов у детей в возрасте от 6-ти до 18-ти лет, по предложенным схемам, в условиях общего обезболивания и стандартним схемам в амбулаторных условиях. Через 2 года после санации полости рта у детей школьного возраста, проведенной в условиях общего обезболивания, осложнения кариеса возникли в 15,67% случаев, преимущественно в зубах с наличием середнего и глубокого кариеса при его остром течении. Оценка эффективности лечения, проведенная через 2 года, свидетельствует о достаточно высокой эффективности предложенных манипуляций и может бать рекомендованой для широкого применения в стоматологической практике.

Ключевые слова: неосложненный кариес, дети, общее обезболивание.

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TREATMENT OF UNCOMPLICATED DENTAL CARIES OF DECIDUOUS TEETH PROVIDING GENERAL ANESTHESIA FOR CHILDREN OF SCHOOL AGE

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The purpose of the present study was to substantiate the amount and sequence of dental manipulations for the treatment of uncomplicated deciduous teeth caries providing general anesthesia for children of school age. A comparative analysis of the deciduous teeth uncomplicated caries treatment results was performed in children aged 6 to 18 years, who had been treated according to the suggested scheme, under general anesthesia and standard charts on an outpatient basis. Over 2 year after the sanitation of oral cavity for children of school age, carried out under the conditions of a general anesthesia, complications of caries arose about in 15,67% of cases, mainly in the teeth with a presence of medium and deep caries in its acute course. Assessment of the treatment efficacy, carried out 2 years later, gives evidence for sufficiently high efficacy of the suggested manipulations and it seems advisable to recommend it for general use in dental practice.

Keywords: uncomplicated caries, children, general anesthesia.

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THE EFFICACY AND SAFETY OF LONG-TERM SYSTEMIC ACYCLOVIR THERAPY OF NEONATAL HERPES IN IMMUNOCOMPETENT CHILDREN

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Medical case histories of two male infants born naturally, in term, who developed neonatal *Herpes simplex virus* type 2 (HSV-2) infections are discussed. Mothers of both infants presented with signs of vesicular rash in the anogenital area at the time of parturitions. In both cases the presented HSV-2 infection had intranatal transmission route. Clinical course of infection was notable for recurrent vesicular rash with no signs of fever or systemic disorders. Both infants were prescribed continuous systemic acyclovir therapy from the early age for over a year. In both cases long-term course of acyclovir was well tolerated and led to long-lasting control of the infection. Therefore such therapeutic regimen might be preferable to the intermittent short-term courses for exacerbations of HSV-1 and HSV-2 infections in infants. Assessment of efficacy and optimal duration of the treatment should be mainly determined by clinical indications.

Key words: neonatal HSV infection, acyclovir, infants, treatment

The study is a fragment of the research project "Immunogenetic predictors of development of diseases associated with latent infections in adults and children", state registration number 0115U001214.

Herpetic infection of newborn, or neonatal herpes (NH), is a rare but potentially lethal disease, which develops prenatally or during the first 4-6 weeks of life. [11] Unless antiviral chemotherapy is used, disseminated form of NH leads to a mortality level of about 80% and high rate of residual disabling damage to the nervous system, eyes and skin in survivors. In newborns who develop NH, administration of extended long-term suppressive antiviral therapy should be considered to reduce the rate of recurrence, and tolerability of such therapies is an issue of special concern. [4,12] Although conventional short-term therapeutic regimens are well-studied and proven to be efficient and have good tolerability, there are limited number of research showing not only efficacy but also safety of continuous suppressive anti-herpetic therapy. [12]

Herpetic infection is transmitted to neonates mostly from mothers with genital herpes which may be caused by both Herpes simplex virus type 2 (HSV-2) and Herpes simplex virus type *1* (HSV-1) infections. [5] An estimated 1 in 3000 to 20,000 live births will be infected with HSV. [6] Both HSV-1 and HSV-2 have the ability of being transmitted from mother to child antenatal, during vaginal delivery (intrapartum way) or after birth by direct skin-to-skin contact. [2] Both mentioned HSV types are able to cause neonatal disease. [3,6] Prevalence of genital herpes is considered to be high due to possible asymptomatic replication of virus thereby contributing to sexual route of transmission. Regarding global

epidemiological data, the total number of people aged 15-49 years (fertility peak) and infected with HSV-2 in 2012 amounted to 417 million globally; genital HSV-1 infection prevalence was estimated at 140 million people worldwide between the ages of 15 and 49 years. [8,9] Currently there is no effective vaccine against HSV 1+2 types available.

Accordingly, NH is a multidisciplinary medical and social problem, which represents a serious potential burden for public health and healthcare systems.

The article presents the medical histories of two male infants with NH who received acyclovir (ACV) orally on regular basis from early age and over a period of 15 months. Consent of legal representatives of patients for data publication is obtained.

Male infant D. (date of birth – October 2nd, 2014) was born from 3rd pregnancy (1st one was ectopic, 2nd resulted in early miscarriage in 2003).

The prenatal course was remarkable for upper respiratory tract infection on the 10th week and high miscarriage risk on the 19th week of pregnancy. The mother reported the occurrence of vesicular lesions in gluteal region immediately before the parturition but no virology or microbiology of vesicle contents were performed at that time and the delivery was carried out in a natural vaginal way at the term of 41 weeks, complicated with uterine inertia.

The child's birth weight was 4200 g; body length – 56 cm; Apgar score was evaluated at 6 - 7 points. Being stable immediately after birth, the condition worsened on the 4th day of life due to development of lethargy, clonic-tonic convulsions and poor feeding, therefore the newborn was transferred to neonatal intensive care unit (ICU).

At this point multiple common blood count and blood chemistry tests, as well as cerebrospinal fluid (CSF) study were performed. Regarding the results, no signs of systemic inflammation were present. Blood, CSF and urine cultures were negative. Chest X-ray, abdominal and heart ultrasound, ECG and neurosonography detected no significant pathology.

Blood serology (ELISA) performed on the 5th day after birth in both the child and the mother revealed anti-HSV type 1+2 Ig G, with avidity index of 100%, while specific anti-HSV Ig M were not detected at that point, neither for the child nor for the mother. The newborn's CSF was negative for HSV type 1 and 2 and cytomegalovirus DNA (qualitative PCR method).

On the 7th day of life scarce papular-vesicular exanthema occurred on the occipital scalp while the general condition improved with no signs of convulsions. On this intravenous ACV was administered in addition to the ongoing antibacterial, antifungal and supportive therapy for 7 days, followed by a short fourteen-day course of oral ACV. Likewise the child received 2 doses of intramuscular specific anti-herpetic homological immunoglobulin. Within the next 3 days after ACV administration, new elements of rash continued to appear, and resolved through crusting in 10 days.

At the time of discharge the patient was stable and had positive weight dynamics.

Afterwards, however, vesicular rash relapsed twice a month. Parents reported no concomitant fever or other systemic symptoms, no recurrence of seizures; the child seemed to be generally well and kept on gaining weight gradually.

Parents asked for consultation about the recurrence of vesicular rash when the infant was 3 month old. PCR testing of vesicle contents was positive for HSV-2 DNA. That substantiated the necessity of long-term course of oral ACV in symptom-dependent dose, which was planned initially for 6-12 months. Basic suppressive dose was 20 mg/kg/day in two fractionated doses, but not more than 400 mg daily. In case of relapse of vesicular rash ACV in the "loading dose" of 80 mg/kg daily in 3 - 4 divided doses were administered for 5-7 days depending on the pace of rash regression and crust formation. [1]

Relapses of vesicular rash occurred on the same area – specifically, in the occipital region of the head (fig. 1). At the onset of systemic ACV therapy vesicular exanthema reoccurred every 10-15 days, was quite abundant and expansive (2-4 mm), often transformed into pustular elements, and lasted for 7 days and more. Relapses were often associated with upper respiratory tract infections. After 90 days of regular ACV intake the "attacks" of rash became less frequent (once in 40-60 days) and manifested in small (1-2 mm) single elements that regressed in 1-2 days with corresponding increase of ACV dosage. Also a painless tight papule sized 1-2 mm was defined against the unchanged skin on the place of recurrences in the occipital region in the attack-free period. Practically it took 15 months to reach a stable result after which the systemic ACV therapy was discontinued. There are no signs of any neurological impairment at present and the boy attends nursery school.

Male infant L. (date of birth – July 15th, 2014) was born from the 4th pregnancy. The first pregnancy ended with the birth of a healthy sibling in 2002, the second and the third were terminated based on the mother's request. The given pregnancy was at risk of spontaneous abortion in the first trimester. At the 27th week of pregnancy, preterm, premature rupture of the membranes occurred causing the outflow of amniotic

fluid, chorioamnionitis and ascending infection of the placenta. Vaginal culture of Klebsiella pneumoniae was obtained and systemic antimicrobial therapy was administered.

After the anhydrous interval of 769 hours and 36 minutes, the labor started prematurely on the 31st week of gestation. On the day of delivery the woman presented with multiply vesicular lesions in the area of labia majora; however, no testing of vesicle contents was performed and thus no correction of obstetric tactics was applied: the newborn was delivered in a vaginal way.

The child was born in serious condition with birth weight of 1940 g and body length of 42 cm. Apgar score was 6 at the one-minute test and 6 at the five-minute test. Respiratory disorders (Downes score – 4 points), neurological impairment (decrease in consciousness and reflexes), along with hemodynamic disorders, and hemorrhagic syndrome jointly resulted in the severity of the condition which required treatment in the neonatal ICU.

From the moment of birth abundant vesicular-pustular rash on the trunk and the scalp as well as symptoms of conjunctivitis were present. However, no testing of vesicle contents was performed in the neonatal ICU as the rash was interpreted as a manifestation of transient neonatal pustular melanosis. The infant received antibacterial therapy for Klebsiella pneumoniae infection, antifungal and supportive therapy, but no antiviral treatment.

After discharge from the hospital at 1.5-month age vesicular lesions continued to occur periodically, twice a month on the average. At the age of three months the child developed keratoconjunctivitis. DNA of HSV-2 was isolated from vesicle contents by PCR method. Accordingly, administration of continuous long-term course of oral ACV in symptom-dependent dose was reasonable.

The clinical course of NH in the patient L. was notable for various sites of relapses: exanthema had no permanent localization and might occur on any area of skin (fig. 2) and even on oral mucosae. During the follow-up period the parents of infant L. made several attempts to discontinue ACV on their own account which resulted into reactivation of the infection in the form of skin rash within 7-10 days from the moment of ACV cessation and forced them to resume ACV treatment. After 18 months of the continual suppressive chemotherapy another parents' attempt of ACV discontinuation led to reactivation of the infection in the form of severe keratoconjunctivitis. Consequently ACV as an agent for systemic antiviral therapy was substituted with valacyclovir. [1] Given the severity of the disease, the therapeutic aim was reconsidered as 1 year symptom-free period. The duration of recent valacyclovir course is 11 months at present (8 months symptom-free).

Duration of continuous enteral intake of ACV for both infants was about 15 months. Both boys tolerated such a long-term ACV therapy quite well, however, during "loading dose" administration single episodes of abdominal cramps and vomiting were registered; the given symptoms had mild to moderate intensity and were fully tolerable.

Laboratory monitoring aimed to control the safety of the therapy was performed at least monthly and included complete blood count and urinalysis, blood chemistry (creatinine, ALT and AST levels) and glomerular filtration rate assessment. During the period of observation all the values of the tests mentioned were within the physiological normal range.

During suppressive antiviral chemotherapy both children started vaccination according to the national "catch-up immunization schedule".

Absence of recurrence of the vesicular pustular rash on the background of the suppressive antiviral chemotherapy for more than 90 days was selected as a target outcome allowing ACV discontinuation. Regarding the further strategy of antiviral chemotherapy after the discontinuation of ACV, it was considered to use the "situational treatment" mode. It implies occasional use of oral ACV and ACV-based ointment locally only for recurrences of HSV.

Discussion. In both presented cases contamination of HSV-2 type is seen as an obstetric infection. However, the form of HSV-2 infection in women at the time of delivery remains unclear, and the issue might be of high clinical value as viremia occurring in primary (acute) infection may cause severe disseminated forms of fetal and newborn disease. Both women considered the given episodes as primary, although, absence of general non-specific signs of acute infection (e.g. fever, chills, malaise etc.) in women at the time of vesicular exanthema manifestation does not allow to exclude reactivation of HSV-2. It should be noted, however, that both pregnant women were immune to HSV-1, which could modify the clinical picture of genital herpes, as these specific antibodies provide partial cross protection against HSV-2. [10]

A special trait of both given cases were a relapsing course of NH, which were relatively well controlled by long-term use of oral ACV only, but the pathogenesis of such recurrence is an issue to discuss.

Whereas, patient L. had recurrences of vesicular rash occurring in the area of various dermatomes, patient D. had them exclusively on the occipital scalp. Amount and localization of herpetic lesions during reactivation depends on the number of infected paravertebral ganglia in which HSV persists. [13] The

prolonged anhydrous period might led to a massive penetration of HSV-2 affecting a large number of ganglia in patient L. In addition, the total area of herpetic lesions in women at the time of delivery is unknown, that does not allow to exclude high infectious dose of HSV-2 in each case given.

It should also be noted that autoinoculation of virus present in the case is not typical for most infected patients as production of antibodies prevents it. Activated HSV-specific CD8+ T-cells are normally stored in the infected sensory ganglia, inhibiting viral reactivation by production of IFN-γ, which was presumably not applicable in these cases. [14] Regarding that there might be adaptive immunity malfunction in combination with cellular immune malfunction in patient L. and probably in patient D.

Transient age-related increase of adenosine might also be relevant. It elevates the amount of intracellular cAMP and thus causes a suppression of T-helper type 1 and reduction of IFN-α, IFN-β and IL-12 production, in consequence degrading neutralization of HSV-infection in sensory ganglia. [7]

The proven fact is that cellular immunity is a priority for "controlling" HSV infection, but which of the viral antigens (glycoproteins) is the most important inducer of defense reactions remains unknown. [14] The incomplete expression of HSV antigens potentially helps to avoid its suppression by T-cell immunity. Furthermore, relapses of vesicular rash occurring against the ongoing suppressive antiviral chemotherapy, may be linked to HSV resistance to ACV.

Presently none of the known antiviral agents is able to completely eliminate HSV infection. Therefore, the main therapeutic objective is to reduce the duration and severity of primary (acute) infection, and to prevent relapses in persistent infection (i.e. suppressive therapy). However, while the criteria for initiating antiviral chemotherapy in newborns and infants are clearly defined for acute infection, the recommendations for suppressive therapy are inexact and conflicting. [12] Accordingly, standardized laboratory and clinical criteria for initiation the antiviral therapy, precise targets of therapy and clear criteria of effectiveness are needed. Considering the fact that the intensity of specific humoral immunity does not affect the intracellular replication of HSV and a phenomenon of viremia is hard to be detected even in case of HSV reactivation, evaluation of "viral load" and the titer of specific antibodies are not suitable as criteria for the start and/or termination of specific chemotherapy. [13] For these purposes, determining the specific NK-cell levels (activity) and/or expression of specific viral antigens reflecting the activity of the HSV replicative DNA is seen as an optimal tactics.

It should also be emphasized that the recommended pediatric dosages of ACV had considerable therapeutic effect and was well-tolerated during long-term administration without neither the necessity of dose revision or monitoring plasma levels of the medication used (which was beneficial regarding current conditions of "limited laboratory resources"), nor cancellation the chemotherapy or using any correcting medications. However, it should be considered that ACV discontinuation in disseminated recurrent forms of HSV infection may in some cases lead to viral reactivation resulting in unpredictable systemic disorders.

Conclusions

1. ACV is the first-choice medication for treatment of NH in neonates and infants. According to our observations, long-term ACV therapy is well tolerated in children, and therefore may be more rational than short-term courses used only for suppressing HSV-1 and HSV-2 infection on exacerbations.

2. Evaluation of the efficacy of treatment and the possibility of discontinuation of ACV in infants are determined by clinical indications, e.g. suppression of herpetic exanthema relapses for not less than 90 days.

3. Cancellation of ACV after a long-term therapy might cause HSV reactivation with the development of systemic lesions, in particular, keratitis.

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Реферати

ЕФЕКТИВНІСТЬ І БЕЗПЕКА ТРИВАЛОЇ СИСТЕМНОЇ ТЕРАПІЇ НЕОНАТАЛЬНОГО ГЕРПЕСУ АЦИКЛОВІРОМ У ІМУНОКОМПЕТЕНТНИХ ДІТЕЙ

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Представлено обговорення двох клінічних випадків новонароджених чоловічої статі, народжених природним шляхом, в термін, у яких розвинулась неонатальна герпетична інфекція (вірус простого герпесу 2 типу (HSV-2)). У матерів обох пацієнтів були ознаки везикулярного висипу в аногенітальний області під час пологів. В обох випадках HSV-2 інфекція мала інтранатальний шлях передачі. Клінічний курс інфекції відрізнявся рецидивуючим везикулярним висипом без ознак лихоманки або системних розладів. Обом пацієнтам з раннього віку була призначена безперервна системна терапія ацикловіром на період більше одного року. В обох випадках переносимість тривалого курсу ацикловіру була доброю і був досягнутий тривалий контроль інфекції. Таким чином, подібний терапевтичний режим може бути кращим за переривчасті короткострокові курси при загостреннях інфекцій HSV-1 і HSV-2 у немовлят. Оцінка ефективності і оптимальної тривалості лікування повинна визначатися в основному клінічними показаннями.

Ключові слова: неонатальний герпес, ацикловір, діти, терапія

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ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ ДЛИТЕЛЬНОЙ СИСТЕМНОЙ ТЕРАПИИ НЕОНАТАЛЬНОГО ГЕРПЕСА АЦИКЛОВИРОМ У ИММУНОКОМПЕТЕНТНЫХ ДЕТЕЙ

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Представлено обсуждение двух клинических случаев новорожденных мужского пола, рожденных естественным путем, в срок, у которых развилась неонатальная герпетическая инфекция (вирус простого герпеса 2 типа (HSV-2)). У матерей обоих пациентов были признаки везикулярной сыпи в аногенитальной области во время родов. В обоих случаях HSV-2 инфекция имела интранатальный путь передачи. Клинический курс инфекции отличался рецидивирующей везикулярной сыпью без признаков лихорадки или системных расстройств. Обоим пациентам с раннего возраста была назначена непрерывная системная терапия ацикловиром на период более одного года. В обоих случаях переносимость длительного курса ацикловира была хорошей и был достигнут длительный контроль инфекции. Таким образом, подобный терапевтический режим может быть предпочтительнее прерывистых краткосрочных курсов при обострении инфекций HSV-1 и HSV-2 у младенцев. Оценка эффективности и оптимальной продолжительности лечения должна определяться в основном клиническими показаниями.

Ключевые слова: неонатальный герпес, ацикловир, дети, терапия

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COMPARATIVE CLINICAL EFFICIENCY ASSESSMENT OF VARIOUS LOCAL ANESTHESIA METHODS IN CURING DENTAL CARIES AND PULPITIS.

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The clinical efficacy comparison of various local anesthesia methods was carried out in 109 patients with acute deep caries of teeth, 18 - with pulmonary hyperemia and acute traumatic pulpitis, and 25 – with acute and chronic pulpitis forms requiring local anesthesia for dental treatment. The total of 30 healthy individuals with a lack of carious lesions and pulpitis of similar teeth groups and the identical age group served as controls. For the efficient management of local anesthesia during the outpatient treatment of patients with acute deep caries of teeth, pulmonary hyperemia and acute traumatic pulpitis, the biological method for maintaining the viability of the pulp and its functions has proven the superiority of the intraosseous anesthetic method. In our opinion, anesthesia of dental manipulations in patients with acute and chronic pulpitis forms by extirpation method should be carried out by the infiltration, conduction and intraosseous methods of amide anesthetics administering with vasoconstrictor concentration of 1: 100000, which prevent pulp bleeding during treatment.

Key words: teeth caries, pulpitis, local anesthesia.

The study is a fragment of the research project "Features of the course, therapeutic and diagnostic tactics and prevention of hard tooth tissues diseases, periodontal and mucous membrane of the oral cavity under the influence of local and general factors", state registration number 0113U006438 (2013-2018).

The most common among dental diseases is dental caries and its complications, which according to WHO affect about 90% of the population. Especially sharply caries grew among the population in the last century, which can be associated with living conditions and work, as well as with the nature of the diet. Acute deep caries and pulmonary disease are accompanied by different nature and intensity of pain.

The problem of pain and anesthesia of painful manipulations in dental caries and pulpitis treatment, remains relevant despite the large number of studies [3, 5]. This is due to the fact that modern dentistry