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Review

Neurogenic heterotopic ossification: A review. Part 2

Vladimir A. Novikov, Alina M. Khodorovskaya, Valery V. Umnov, Evgenii V. Melchenko, Dmitry V. Umnov

H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: Neurogenic heterotopic ossification is characterized by the formation of bone tissue in the soft tissues of the body caused by severe brain or spinal cord injury of various etiologies. In neurogenic heterotopic ossification, the hip joints are most often affected.

AIM: To analyze publications on the instrumental diagnosis, surgical and nonsurgical methods of treatment, and prevention of neurogenic heterotopic ossification of the hip joints.

MATERIALS AND METHODS: In the second part of our review, we analyzed the literature on modern diagnostics, surgical and conservative methods of treatment, prevention of the formation and recurrence of neurogenic heterotopic ossification of the hip joints. Data were searched in scientific literature databases, namely, PubMed, Google Scholar, Cochrane Library, CrossRef, and eLibrary, without language restrictions.

RESULTS: Modern diagnostic methods allow the screening of hip neurogenic heterotopic ossification in patients at high risk of their formation, with further verification of the diagnosis by computed tomography or magnetic resonance imaging. Despite the lack of consensus on the timing of hip neurogenic heterotopic ossification removal at present, surgical treatment is the most effective method, which allows the removal or reduction of the volume of neurogenic heterotopic ossification. Most cases require controlling the pain syndrome and improving the quality of life of the patients. Despite the common etiologic factor (damage to the central nervous system), nonsurgical methods of the prevention and treatment of patients with neurogenic heterotopic ossification of the hip joints have different effectiveness because of spinal cord injury, cerebral trauma, and cerebral palsy.

CONCLUSIONS: Randomized controlled trials will help to establish the efficacy of conservative treatment methods to prevent the formation and recurrence of hip joint neurogenic heterotopic ossification, taking into account the cause of central nervous system lesions.

Keywords: neurogenic heterotopic ossification; diagnosis of neurogenic heterotopic ossification; hip joints; radiation therapy; nonsteroidal anti-inflammatory drugs; bisphosphonates.

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Научный обзор

Нейрогенная гетеротопическая оссификация. Обзор литературы. Часть вторая

В.А. Новиков, А.М. Ходоровская, В.В. Умнов, Е.В. Мельченко, Д.В. Умнов

Национальный медицинский исследовательский центр детской травматологии и ортопедии имени Г.И. Турнера, Санкт-Петербург, Россия

АННОТАЦИЯ

Обоснование. Нейрогенная гетеротопическая оссификация — это образование костной ткани в мягких тканях организма, возникающее в результате тяжелого повреждения головного или спинного мозга различной этиологии. При нейрогенной гетеротопической оссификации чаще всего поражаются тазобедренные суставы.

Цель — проанализировать публикации, посвященные инструментальной диагностике, хирургическим и нехирургическим методам лечения и профилактике нейрогенной гетеротопической оссификации тазобедренных суставов.

Материалы и методы. Во второй части обзора проанализирована литература, посвященная современной диагностике, хирургическим и консервативным методам лечения, профилактике образования и рецидивов нейрогенной гетеротопической оссификации тазобедренных суставов. Поиск данных проводили в базах научной литературы PubMed, Google Scholar, Cochrane Library, Crossref, eLibrary без языковых ограничений.

Результаты. Современные методы диагностики позволяют проводить скрининг нейрогенной гетеротопической оссификации тазобедренных суставов у пациентов с высоким риском их формирования, с последующей верификацией диагноза с помощью компьютерной или магнитно-резонансной томографии. Несмотря на отсутствие в настоящее время единого мнения о сроках удаления нейрогенной гетеротопической оссификации тазобедренных суставов, хирургическое лечение — наиболее эффективный метод, позволяющий ее удалить или уменьшить объем. В большинстве случаев удается купировать болевой синдром и улучшить качество жизни пациентов. При общности этиологического фактора (повреждение центральной нервной системы) эффективность нехирургических методов профилактики и лечения различная у пациентов с нейрогенной гетеротопической оссификацией тазобедренных суставов вследствие травмы спинного мозга, черепно-мозговой травмы и детского церебрального паралича.

Заключение. Рандомизированные контролируемые исследования позволят установить эффективность консервативных методов лечения для профилактики формирования и рецидивов нейрогенной гетеротопической оссификации тазобедренных суставов с учетом причины поражения центральной нервной системы.

Ключевые слова: нейрогенная гетеротопическая оссификация; диагностика нейрогенной гетеротопической оссификации; тазобедренные суставы; лучевая терапия; нестероидные противовоспалительные препараты; бисфосфонаты.

Как цитировать

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BACKGROUND

Heterotopic ossification (HO) is the pathological formation of bone tissue outside the skeleton in tissues not connected by continuity with the originally determined skeletogeny mesenchyme [1]. HO has various causes, including hereditary diseases such as progressive ossifying fibrodysplasia and acquired conditions resulting from trauma and burns [2].

Neurogenic heterotopic ossification (NHO) is a separate form of HO that results from severe brain or spinal cord injury (SCI) of various causes [3]. NHO most often affects the hip joints [4, 5]. Our literature review [6] analyzed the epidemiology, risk factors for the formation, pathogenesis, clinical presentation, and laboratory diagnosis of NHO.

This study **analyzed** publications devoted to instrumental diagnosis, surgical and nonsurgical methods of treatment, and prevention of NHO of the hip joints.

MATERIALS AND METHODS

Data were searched in several databases, including PubMed, Google Scholar, Cochrane Library, Crossref, and eLibrary, without language restrictions. The search spans 50 years. This article was written following information analysis and synthesis. Because of the specificity of NHO, most materials focus on the pathologic process surrounding the hip joints.

RESULTS AND DISCUSSION

Diagnosis of NHO

Radiography is the primary method for diagnosing NHO, which includes the following types [7, 8]:

Radiography of the hip joints and pelvic bones is the most accessible and widely used method for diagnosing HO. Typically, HO is clinically apparent before it is visible on radiographs [4]. HO can only be diagnosed radiologically three–six weeks after the onset of the first clinical symptoms [2, 3].

Multispiral computed tomography (CT) of the hip joints, similar to radiography, is not highly specific, but with similar time of HO visualization. Therefore, this method cannot be used for the early diagnosis of the disease process [7]. However, compared with conventional radiography, this technique allows the visualization of HO in the bone 3D mode, enabling both the diagnosis of the pathology and detailed preoperative planning [8].

Large arteries maintain their diameter even when completely surrounded by ossifications, unlike veins that can be compressed by HO [9]. Therefore, CT angiography is performed to assess the specific location of arterial vessels in relation to HO [10], which contributes to the selection of the optimal surgical access for NHO removal.

Traditionally, *technetium-99 three-phase bone scintigraphy* is the most sensitive method for the early detection of HO. This method allows for the earliest verification of the diagnosis, as early as two weeks after the appearance of clinical symptoms [11]. The first two phases of HO formation are the most sensitive for the early detection of HO, occurring two–three weeks after the appearance of clinical symptoms. Radiopharmaceuticals accumulate in the third phase of HO formation, which occurs four–six weeks after injury. The concentration of the radiopharmaceutical reached its peak within two months and then gradually decreased. A decrease in the accumulation of radiopharmaceuticals is noted after approximately 12 months; however, it can persist even in the chronic mature phase of HO [12]. A disadvantage of scintigraphy is the need to take a radiopharmaceutical. In addition, the method has low specificity, which can lead to difficulties in differentiating HO from other bone processes such as inflammation, trauma, or degeneration. These processes also exhibit increased osteoblastic activity and absorption of osteotropic radionuclides [13]. Currently, many experts believe that scintigraphy is not the preferred method for diagnosing HO because more effective and safer methods have been developed [2, 14].

During the acute phase of HO formation, *magnetic resonance imaging (MRI)* reveals increased vascularization and tissue density. HO is identified on MRI by its isointense or hyperintense signal relative to the muscles on T1-weighted images and hyperintense signal on T2-weighted images. The zone of low signal in the periphery corresponds to the onset of ossification [15]. Wang et al. described MR patterns characteristic of the initial stage of HO formation, even before ossification. On T2- and T1-weighted postcontrast images of HO in the acute phase, heterogeneously high signal intensity was observed in the affected muscles interspersed with several hypointense linear structures that corresponded to intact muscle fibers. In the plane parallel to these muscle fibers, the affected area has the appearance of a "striated pattern." Relatively hypointense areas with a geometric pattern corresponding to the bundles of intact muscle fibers are present within the lesion with diffusely high signal intensity. A "checkerboard pattern" is observed in the plane perpendicular to the muscle fibers [16]. Recognition of these MR patterns in HO may be useful in the early stages because this condition is often misdiagnosed as osteomyelitis or even sarcoma [15, 16].

Ultrasonography is a sensitive method for visualizing soft tissue injuries and calcifications. As an advantage, it can be applied without the need for patient transportation, which is particularly relevant for bedridden patients [17]. Q. Wang et al. proposed the use of ultrasonography to monitor HO formation. Ultrasonography allows the visualization of the HO in different planes without additional radiation exposure. In addition, based on the values of the "gray scale," it can

quantify the structural changes of HO in different phases of its development [18]. Rosteius et al. (2019) analyzed ultrasound results from 217 patients with NHO and found that the method has a sensitivity of 88.9% in detecting the pathological process on an average of 62.4 days after spinal cord or brain injury [19].

Classification of HO of the hip joints

D.E. Garland [20] proposed a classification of NHO depending on the localization of the ossifications and their etiology:

1. NHO in the area of the thigh-withdrawing muscles is characteristic of patients with consequences of SCI and cerebral stroke, as well as after total hip arthroplasty.
2. Anterolateral NHO is most often observed in patients with the consequences of traumatic brain injury (TBI).
3. Anteromedial NHO is more often found in patients with the consequences of SCI.
4. NHO around the femoral neck observed after total hip arthroplasty.
5. The NHO of the posterior surface of the femur and hip joint is visualized on radiographs in patients who have suffered from TBI and SCI and patients who underwent hip surgeries.
6. The NHO below the medial parts of the hip joint predominantly develops after TBI.

Mavrogenis et al. argued that the NHO classification based solely on anteroposterior radiographs is insufficient for assessing the degree of ankylosis and determining the precise location of the NHO. To address this issue, we propose a classification system for NHO based on CT data of the hip joints and clinical assessment of the degree of ankylosis. The classification system distinguishes anterior, posterior, anteromedial, anterolateral, and circumferential NHO in the hip joint. The purpose of this classification is to optimize surgical access for NHO resection [21]. However, according to M. Arduini et al., the classification proposed by A.F. Mavrogenis et al. did not consider the unique muscle involvement in NHO formation. In their analysis of 55 patients (73 hip joints), they identified seven patterns of hip NHO and justified the use of optimal surgical access for each group of NHO [8]. Similar to M. Arduini's classification, NHO can be categorized into anterior, posterior, anteromedial, and circular patterns, as well as medial, lateral, and posterolateral patterns. For instance, in the medial pattern, which is not included in the classification by A.F. Mavrogenis et al.), only the crestal, short, and large adductor muscles of the thigh are involved in NHO. In this case, the authors recommend using the iliopsoas approach. For NHO of the crestal bone only, the Ludloff approach is recommended [8].

Over the past 50 years, several HO classifications have been proposed in the literature [8, 21, 22]. However, the classification proposed by A.F. Brooker et al. (1973) remains the most widely used.

Class 1 refers to bone islands found in the soft tissue surrounding the proximal femur.

Class 2 refers to bone spurs that originate from either the pelvic or proximal femur, leaving at least 1 cm of space between the opposite bone surfaces.

Class 3 refers to bone spurs that originate from either the pelvis bones or proximal femur but reduce the distance between opposing bone surfaces to <1 cm.

Class 4 refers to hip ankylosis.

Prevention and treatment of NHO

The treatment of NHO typically involves a comprehensive approach. NHO removal is the most effective treatment [2, 3, 9]. Unlike tumors, total resection of the pathological formation is not necessary when resecting HO [9, 14]. Currently, a functional resection is preferable because it increases the amplitude of movements in the hip joint while minimizing traumatization of the surrounding tissues. Hip stiffness in NHO is typically caused by extra-articular factors. In rare instances, restricted range of motion in the hip joint can be also attributed to degenerative changes in the articular surfaces of the hip joint and/or ankylosis of the joint [4, 9, 24].

Surgical treatment is indicated for cases with a progressive decrease in the amplitude of hip joint movements, compression of vascular and nerve structures, and a general decrease in the quality of life [9, 14, 25].

As noted by M.J. Taunton, a pronounced pain syndrome alone cannot be the sole indication for surgical treatment because it may not be caused solely by HO [26]. T.K. Cobb shared a similar perspective and provided clinical examples in which pain syndrome persisted even after the removal of HO from the hip joint [27].

P. Denormandie et al. suggested that quality-of-life deterioration is a significant indication for HO removal. In patients with SCI-induced NHO, the removal of the ossification located on the anterior surface of the femur and hip joint enables the patient to sit up and, if necessary, perform bladder self-catheterization. By removing the HO located on the anteromedial surface of the femur, which is characteristic of patients with TBI consequences, the flexion–adduction–intra-rotational contracture of the hip can be eliminated. This can have a positive effect on patient gait in most cases [14].

Preserving cognitive functions is crucial for the successful surgical removal of NHO and full range of postoperative rehabilitation measures [2]. T.J. Moore noted that patients with severe cognitive impairment experience poor functional outcomes, such as reduced amplitude of movements and NHO recurrence [28].

Currently, no consensus has been established among orthopedists regarding the optimal time frame for NHO

removal. Some authors suggest delaying removal until 12–18 months after the end of growth and HO formation because this may help reduce the recurrence rate [4, 26]. According to F. Genêt et al., signs of NHO immaturity according to scintigraphy should not be considered a contraindication to surgery, particularly in cases where there is a progressive decrease in the amplitude of hip joint movements [25]. Waiting too long can result in significant osteoporosis and coxarthrosis [9, 29]. Early intervention broadens the range of rehabilitation measures [20, 25]. Based on meta-analysis data, Chalidis et al. did not find significant correlations between the risk of HO recurrence in patients with severe traumatic injury and the timing of surgical intervention following trauma. The predicted probability rates of recurrence 13, 21, and 30 months before surgical intervention were 9%, 14%, and 19%, respectively [30]. Although no definitive conclusions can be drawn from this study, the data obtained do not support the claim that early HO excision is associated with a high recurrence risk.

The literature presents clinical and radiologic results of surgical excision of hip NHO in a few series and as single cases. However, all publications note that surgical NHO removal allows for the elimination or reduction of its volume, an increase in the amplitude of hip joint movements, and an improvement in the quality of life. G.A. Macheras et al. reported a statistically significant increase in range of motion and improvement in Harris scale scores in 26 patients (seven patients on the Brooker III scale and 23 patients on the Brooker IV scale) after NHO removal [31]. This is consistent with findings from other studies [28, 32, 33]. However, in cases of hip ankylosis, the postoperative range of motion is significantly lower when surgical intervention is performed after joint ankylosis has formed [5, 25]. This may serve as an additional argument in favor of early surgical treatment for NHO.

Small-sized NHOs without significant clinical symptoms are not removed because of the high risk of complications associated with NHO removal, such as massive blood loss, damage to large arterial and venous trunks and nerves, infection, and femoral and acetabular fractures. Patients with small-sized NHOs are placed under dynamic observation [9, 14, 25].

NHO is characterized by abundant vascularization [34], which can cause significant blood loss during its removal [4, 10]. Intraoperative blood loss during HO removal may increase because of the ruptures of vessels located within the HO thickness [4, 35]. J.H. Kim et al. reported a case of bilateral hip joint ankylosis caused by SCI-induced HO. During HO removal, blood loss was significantly reduced when preoperative embolization was performed on the other hip joint (<500 mL) compared with that when it was not performed (approximately 1500 mL) [35]. In a single-center comparative study, Papalexis et al. evaluated the effectiveness of preoperative embolization for hip NHO. Of the 16 patients who underwent surgical resection of hip NHO, eight received preoperative embolization of the arteries supplying NHO, whereas the remaining eight in the control group did not receive it. In patients who underwent preoperative embolization, the mean intraoperative blood loss was 875 ± 320 mL, which was significantly lower ($p = 0.035$) than that in the control group (1350 ± 120 mL). In addition, a statistically significant decrease ($p = 0.014$) in the hospital stay was found because of lower blood loss. In patients who underwent preoperative embolization, the length of hospital stay was 6.4 ± 1.6 days, whereas in patients who did not undergo embolization, the length of hospital stay was 11.5 ± 1.4 days. Therefore, preoperative embolization before HO resection can significantly reduce intraoperative blood loss and length of hospital stay [36]. However, no literature is available on the indications and contraindications for preoperative embolization in any hip HO.

Damage to the sciatic nerve in NHO has been reported in 3.8%–5.6% of cases because it was completely surrounded by heterotopic tissue [31]. As suggested by P. Koulouvaris et al., intraoperative stimulation can help identify the sciatic nerve and reduce the risk of damage [37].

The incidence of intraoperative fractures of the femoral neck during HO excision is quite high, particularly in hip ankylosis. According to F. Genêt et al., the incidence was 13.7% [24]. In cases of femoral neck fracture at various stages of surgery, the need for one-stage joint endoprosthesis may arise [14]. Currently, alternative options for addressing this issue include resection of the proximal femur or femoral osteosynthesis using an intramedullary rod [14, 31].

The incidence of infectious postoperative complications ranges from 9% to 38% [9, 38]. Gatin et al. suggested that patients with SCI are at a higher risk of infectious complications after HO removal than those with severe TBI [38], which is consistent with the results of other studies [4, 39]. L. Gatin identified additional risk factors for developing infectious complications after HO removal. These include age 30 years and class ⩾III on the ASA scale, which indicates a severe somatic condition [38]. According to l'Escalopier et al., patients with bedsores and inflammatory urinary tract diseases are at an increased risk of postoperative complications. The authors suggest that urine cultures should be sterile before HO removal, particularly in patients with SCI-related complications [9].

The rates of NHO recurrence vary widely, ranging from 0% to 92%. This variability may be due to the authors not specifying the nature of the recurrence, whether it is symptomatic and requires repeated surgical intervention or detected incidentally on radiographs during follow-up [9].

According to most authors, the recurrence rate of HO is independent of its etiology, age, severity of the neurologic deficit, multiplicity, NHO volume [25, 29], and volume of

HO resection [9, 38]. However, S.L. Stovner suggested that patients with SCI have a higher risk of HO recurrence than those with TBI [39]. According to N. de l'Escalopier et al., postoperative hematomas and local inflammatory changes are risk factors for NHO recurrence [9].

Various pharmacologic and nonpharmacologic methods are currently used to prevent HO recurrence and formation in high risk patients [2, 3].

Early rehabilitation. The necessity of early physical activity in patients with HO of various etiologies is a topic of debate.

According to Y. Xu, at the early stage of HO, any mechanical stimulation can activate pluripotent differentiation of mesenchymal stem cells in soft tissues. For instance, mTORC1 can activate resting stem cells and promote chondrogenesis and osteogenesis, which leads to the initiation of HO formation [40]. In an experimental mouse model, A.K. Huber et al. demonstrated that joint immobilization nearly completely inhibited HO by reducing mechanotransduction signals. Therefore, further chondrogenic differentiation of mesenchymal stem cells was not activated [41]. Furthermore, some authors suggested that individuals who participate in sports may be more prone to HO formation [42]. This is due to the increased likelihood of injuries and excessive stretching of soft tissues, which can stimulate the activation and subsequent differentiation of stem cells [40]. C.M. Crawford analyzed the results of early rehabilitation treatment of patients with burn injuries. The study revealed that patients who performed active and passive motor exercises beyond the limit of painless amplitude of movements in the joint had a higher risk of HO formation. Subsequently, they experienced a progressive decrease in the amplitude of movements, leading to ankylosis of the joint caused by HO formation. In a previous study [43], patients who participated in a rehabilitation program that included exercises aimed at stretching their muscles to the point of mild discomfort achieved satisfactory recovery of their range of motion.

O. Daud et al. found a correlation between delayed onset of passive movements in paralyzed limbs and increased NHO incidence. Therefore, early motor therapy must be prioritized to prevent joint contractures and subsequent NHO [3, 29, 44].

Radiation therapy. It is often used to prevent HO formation by targeting osteoprogenitor cells in soft tissues. This is based on the assumption that these cells have high mitotic activity and are sensitive to radiation therapy [45]. In vitro experiments have demonstrated that radiation therapy inhibits the osteogenic differentiation of mesenchymal stem cells. This inhibition is accompanied by a decrease in RUNX2 expression [46], suppression of bone morphogenetic protein (BMP-2) activity, decreased proliferation, and differentiation of osteoblasts and contributes to their apoptosis [47]. Radiation therapy is used in NHO to prevent HO formation and as an independent method of treatment [7, 48].

In their analysis of the efficacy of prophylactic radiation therapy at a dose of 7.5 Gy before resection of the proximal epiphysis of the femur in infantile cerebral palsy, E. Davis et al. found that during the follow-up period of 0.2–17.1 years, NHO occurred in 6 out of 17 (35%) patients with radiation therapy and 15 out of 18 (83%) operated hips in patients without radiation therapy [49].

A.C. Museler et al. reported the results of using radiation therapy for hip NHO in 244 patients with SCI during the initial phase of HO formation. The diagnosis was confirmed by MRI after an initial ultrasound examination of the hip joints. Only 13 (5.3%) patients showed progression of HO growth after one session (7 Gy) of radiation therapy, followed by another session (7 Gy). Of these 13 patients, only one required surgical intervention because of ankylosis of the hip joint [50]. However, because of the wide range of follow-up periods (14–505 days), determining the absence of recurrence in patients with a short follow-up period is difficult [51].

C.H. Lee et al. reported that radiation therapy with a total dose of 20 Gy led to regression of pain syndrome in patients with hip NHO and normalization of alkaline phosphatase activity. However, the authors presented data on the treatment of only three patients with NHO resulting from various brain lesions, and the follow-up period was limited to 6 months [52].

To prevent the recurrence of HO of nonneurogenic etiology, combined treatment (surgery and radiation therapy) produces significantly better results than HO removal [53, 54].

When comparing the results of combined treatment of HO in the hip joints of patients with neurogenic, nonneurogenic, and mixed etiologies, T. Ebinger et al. found a similar frequency of recurrences in the groups in 5 years of outpatient follow-up [55].

Currently, no conclusive evidence supports the greater efficacy of radiation therapy as a method of recurrence prevention when applied preoperatively or postoperatively in patients with HO of different etiologies [48, 56]. T. Honore et al. also conducted a retrospective analysis of data from 95 patients with NHO after SCI and traumatic injury. They concluded that prophylactic radiation therapy before surgical removal of NHO of the hip joint is associated with a high risk of postoperative sepsis and does not reduce the NHO recurrence rates [57], which is consistent with the findings of C. Cipriano et al. [58].

The long-term effects of radiotherapy for NHO are poorly understood; however, the results of large randomized trials suggest the lack of oncologic risk [48, 56]. Nevertheless, Mourad et al. described the development of undifferentiated femoral sarcoma after radiotherapy for recurrent hip HO of traumatic etiology 16 months after the second course [59]. M.K. Farris et al. also reported an osteosarcoma of the pelvic bones diagnosed 11 years after a single course of radiotherapy for traumatic hip HO [60].

Nonsteroidal anti-inflammatory drugs (NSAIDs). One of the putative mechanisms of HO formation is the excessive production of prostaglandins, which are involved in the regulation of the differentiation of mesenchymal cells into osteoblasts and indirectly affect the expression of bone morphogenic proteins. NSAIDs, which inhibit cyclooxygenase, reduce the synthesis of prostaglandins, prostacyclin, and thromboxane and thus may prevent ossification [61].

In 2001, K. Banovac et al. published the results of a randomized, prospective, double-blind, placebo-controlled study in 33 patients evaluating the efficacy of indomethacin at a dose of 75 mg daily for three weeks after SCI for NHO prevention. A significant reduction in the incidence of NHO was found in the indomethacin group compared with placebo ($p < 0.001$) [62]. In 2004, K. Banovac published the results of another prospective, double-blind, placebo-controlled study in 76 patients evaluating the effect of rofecoxib, a selective inhibitor of cyclooxygenase-2. The results showed that the incidence of NHO formation was statistically significantly reduced in the rofecoxib group compared with the placebo group [63]. Data from a systematic review by S.Y.N. Schincariol et al. suggested that the early use of NSAIDs after SCI is effective in preventing HO development [51]. This correlates with the data of E.C. Zakrasek et al. who showed a significantly lower likelihood of HO development in patients with SCI who received NSAIDs for ⩾15 days in the first 60 days after SCI than patients who did not receive such treatment [64]. Results of a systematic review and meta-analysis by Y.U. Yolcu et al. added to the overall positive impression regarding the efficacy of NSAIDs in NHO prevention. Although the authors did not find sufficient evidence to demonstrate a statistically significant benefit of known prophylactic medications in preventing NHO compared with placebo, an analysis of data on NSAID use found a significantly lower incidence of NHO with NSAID use than with placebo [65].

According to J. Dartnell et al., NSAIDs are not effective in preventing HO in high-risk patients, particularly adolescents with cerebral palsy, after proximal femoral resection. In a group of 21 patients who took indomethacin at a dose of 0.5 mg/kg within 10 days after surgery and in a group of 21 patients who did not take indomethacin, symptomatic HO was found in five patients over a follow-up period of 4.5 years, and in the group of 21 patients who did not take indomethacin, symptomatic HO was found in five patients over a follow-up period of 4.3 years. Based on these data, the authors believed that the use of indomethacin was inappropriate for HO prevention in this group [66].

In addition, NSAIDs are associated with both significant gastrointestinal side effects and an increased risk of fracture nonunion and development of march fractures in patients. The risk of nonunion of fractures increases when NSAIDs are used for >2 weeks at high doses, which limits their use in patients with polytrauma [67].

Bisphosphonates. Bisphosphonates are antiresorptive agents that induce osteoclast apoptosis and inhibit calcification. According to some authors, bisphosphonates can be considered a means of preventing NHO [68, 69]. In a prospective double-blind study, S.L. Stover et al. found that etidronic acid (first-generation bisphosphonates) may inhibit NHO development by suppressing bone mineralization. Based on the analysis of the results obtained, the authors believe that etidronic acid therapy initiated within 60 days after traumatic SCI is more effective than that initiated 60 days after the injury [68]. This is consistent with the data by G. Spielman et al. who indicated the efficacy of etidronic acid in preventing HO in patients following severe TBI [70]. However, K. Banovac believed that if HO was detected by scintigraphy, even in the absence of radiographic signs, etidronic acid did not have the desired effect [71]. According to some authors, etidronic acid does not stop HO development but only slows down matrix mineralization, and at the end of bisphosphonate administration, bone matrix mineralization, i.e., HO growth, continues [72, 73].

In addition to the first generation, subsequent generations of bisphosphonates act only on osteoclasts and are less able to inhibit HO [40].

A. Ploumis et al. reported that the prophylactic use of alendronic acid (second-generation bisphosphonate) in patients with early SCI did not reduce the risk of HO formation. According to the authors, there was an unexpected tendency to form contractures in patients after the use of alendronic acid compared with the placebo group [74].

P. Schuetz et al. believe that pamidronic acid (second-generation bisphosphonate) may be an effective means of preventing HO recurrence after its resection. However, this statement is based on the results of the treatment of five patients with SCI and a follow-up period of 5–54 months [75].

Based on data from a meta-analysis of the pharmacological prevention of HO, Y.U. Yolcu et al. found no statistically significant differences in HO detection when bisphosphonates were administered ($p = 0.58$) [65]. Overall, the evidence to recommend bisphosphonates as a therapeutic agent for preventing HO is inconclusive [51].

CONCLUSIONS

Modern diagnostic methods allow screening for hip NHO in patients at high risk for its formation based on ultrasound findings with further confirmation of the diagnosis by CT or MRI.

Despite the lack of consensus on the timing of hip NHO removal, surgical treatment appears to be the most effective method to remove or reduce the NHO volume, in most cases to control the pain syndrome, and improve the quality of life of patients at risk for postoperative complications and recurrence. In the current scientific literature, no convincing

data have been found on effective pharmacologic prophylaxis of NHO formation and recurrence in patients after TBI, whereas the use of NSAIDs in patients with TBI consequences reduces NHO recurrence. Published data on the efficacy and safety of radiation therapy for NHO are conflicting. No study has analyzed the long-term results of treatment of hip NHO with radiotherapy; therefore, it is impossible to determine the indications and contraindications for this treatment method in patients with NHO. Despite the common etiological factor (damage to the central nervous system), varying efficacies of nonsurgical methods of NHO prevention and treatment in patients with SCI, TBI, and cerebral palsy have been noted. Conducting randomized controlled trials will help determine the effectiveness of these treatment methods in preventing NHO formation and recurrence, considering the nature of the central nervous system lesion. A promising direction for the pharmacological prevention and treatment of NHO may be selective action on various links of NHO pathogenesis in patients with the consequences of damage to the central nervous system.

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AUTHOR INFORMATION

Vladimir A. Novikov, MD, PhD, Cand. Sci. (Med.);
ORCID: 0000-0002-3754-4090;
eLibrary SPIN: 2773-1027;
e-mail: novikov.turner@gmail.com

*** Alina M. Khodorovskaya**, MD, Research Associate;
address: 64-68 Parkovaya str., Pushkin,
Saint Petersburg, 196603, Russia;
ORCID: 0000-0002-2772-6747;
eLibrary SPIN: 3348-8038;
e-mail: alinamyh@gmail.com

Valery V. Umnov, MD, PhD, Dr. Sci. (Med.);
ORCID: 0000-0002-5721-8575;
eLibrary SPIN: 6824-5853;
e-mail: umnovvv@gmail.com

Evgenii V. Melchenko, MD, PhD, Cand. Sci. (Med.);
ORCID: 0000-0003-1139-5573;
eLibrary SPIN: 1552-8550;
e-mail: emelchenko@gmail.com

Dmitriy V. Umnov, MD, PhD, Cand. Sci. (Med.);
ORCID: 0000-0003-4293-1607;
eLibrary SPIN: 1376-7998;
e-mail: dmitry.umnov@gmail.com

ОБ АВТОРАХ

Владимир Александрович Новиков, канд. мед. наук;
ORCID: 0000-0002-3754-4090;
eLibrary SPIN: 2773-1027;
e-mail: novikov.turner@gmail.com

*** Алина Михайловна Ходоровская**, научный сотрудник;
адрес: Россия, 196603, Санкт-Петербург,
Пушкин, ул. Парковая, д. 64–68;
ORCID: 0000-0002-2772-6747;
eLibrary SPIN: 3348-8038;
e-mail: alinamyh@gmail.com

Валерий Владимирович Умнов, д-р мед. наук;
ORCID: 0000-0002-5721-8575;
eLibrary SPIN: 6824-5853;
e-mail: umnovvv@gmail.com

Евгений Викторович Мельченко, канд. мед. наук;
ORCID: 0000-0003-1139-5573;
eLibrary SPIN: 1552-8550;
e-mail: emelchenko@gmail.com

Дмитрий Валерьевич Умнов, канд. мед. наук;
ORCID: 0000-0003-4293-1607;
eLibrary SPIN: 1376-7998;
e-mail: dmitry.umnov@gmail.com

* Corresponding author / Автор, ответственный за переписку