Prophylaxis and treatment of heterotopic ossifications after total hip arthroplasty – contemporary view and proposition of the algorithm

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Abstract

Heterotopic ossification (HO) is the abnormal formation of mature bone in extraskeletal soft tissues, which may commonly occur after Total Hip Arthroplasty (THA). Despite the high incidence of HO and multiple clinical studies examining the phenomenon, the pathophysiology and etiology of HO remain unclear. In advanced cases, HO may significantly decrease results of surgery by impairing range of motion in joint and induce pain. For now, no prophylaxis protocol for prevention of HO in patients after THA exists. Nonsteroidal anti-inflammatory drug (NSAID) treatment and localized low-dose irradiation are currently available only as prophylaxis of HO formation. The authors, conducted a review summing present state of view in case of diagnosis and prophylaxis of HO occur-rence in different clinical cases of patients qualified for Total Hip Arthroplasty.

Key words: heterotopic ossification, total hip arthroplasty, non-steroid anti-inflammatory drugs, radiotherapy

Streszczenie

Skostnienia heterotopowe (HO) są definiowane jako formowanie się dojrzałej tkanki kostnej w tkankach miękkich. Zjawisko stosunkowo często występuje po Aloplastykach Stawów Biodrowych. Pomimo dość dużej prevalencji zjawiska i znaczną ilość badań, etiologia powstawania zmian wciąż nie jest całkowicie wyjaśniona. W zaawansowanych klinicznie przypadkach, HO mogą znacznie wpływać na pogorszenie wyników operacji poprzez zmniejszenie ruchomości stawu oraz nasilenie dolegliwości bólowych. Obecnie nie istnieje algorytm postępowania w profilaktyce powstawania skostnień okołostawowych. Znane metody o udowodnionej skuteczności to profilaktyka z wykorzystaniem niesteroidowych leków przeciwzapalnych oraz radioterapia o niskich dawkach promieniowania. W artykule przeglądowym, autorzy podsumowują obecny stan wiedzy dotyczący profilaktyki występowania skostnień okołostawowych po THA oraz proponują algorytm postępowania w różnych przypadkach klinicznych.

Słowa kluczowe: skostnienia okołostawowe, całkowita aloplastyka stawu biodrowego, niesteroidowe leki przeciwzapalne, radioterapia

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Introduction

Heterotrophic ossification (HO) was described for the first time in 1692 by a French doctor Guy Patin [1]. During World War I, other French scientists, Dejerine and Ceillier, identified “paraosteoarthropathy” among post-traumatic paraplegic soldiers [2].

HO is believed to be the most common complication of total hip arthroplasty (THA) and acetabulum fracture [3-5]. Piriformis ossification is a pathological process which leads to osseous formation at sites which normally do not exhibit properties of ossification [6,7]. HO develops most frequently around the cervical component of the femoral prosthesis (4) and it must be properly differentiated from soft tissue calcifications in this area during which osteoblasts are not activated (3) [8,6]. The prevalence of HO ranges between 5% and 90% (5,6,7) among high risk patients (9-11). It is to be noted that such a big statistical difference results from patient selection, varying observation periods, post-operative application of non-steroidal anti-inflammatory drugs, surgical approach and use of different classifications (3,8). However, only in 7% of cases, osseous formation is advanced enough to lead to a complete loss of movement in the joint, mainly internal rotation, or to pain [11, 12]. Other HO consequences involve compression on the veins masquerading as deep thrombophlebitis and nerve root compression syndrome [13,14].

The aetiology of HO can be divided into three main causes: neurological, genetic and traumatic, which involves orthopaedic procedures [15]. Despite known aetiology, HO pathophysiology still remains unclear. Many possible causes of osseous formation have been raised, such as prostaglandin 2 (PGE-2) activity, hypercalcaemia, tissue hypoxia, increased activity of the autonomic nervous system, dis-equilibrium of parathyroid hormone and calcitonin axis [16]. All these factors contribute to inappropriate differentiation of pluripotent mesenchymal stem cells [15]. Moreover, risks factors for HO during hip arthroplasty have been identified. They include a previous history of HO, post-traumatic degeneration, osteoarthritis, ankylosing spondylitis, osteonecrosis, Paget's disease, male gender, hip joint ankylosis and Forestier's disease [17,18,19]. On the other hand, patients with rheumatoid arthritis showed a diminished risk of HO. It is believed that HO is determined by systemic factors and by local tissue changes, such as inflammation [20], and cell death [21] and upregulation of mineralization growth factors [22-24]. Both inflammation and apoptosis may result in alterations in the pH, which promote the deposition of calcium in the form of hydroxyapatite crystals. Growth factors such as bone morphogenetic protein (BMP) stimulate mineralization and bone formation by their effects on osteoblast progenitor cells [25].

Clinical symptoms and diagnostics

HO occurs typically without symptoms and signs and it may be found incidentally in a follow-up imaging examinations. When HO starts causing complaints, most often they are range from a limited range of motion in the joint to its complete stiffness. It may also trigger local pain, and superficial localized lesions characterized by increased local temperature, mild swelling and erythema [13].

The ultrasound examination of the area near the prosthesis and SPECT CT [26] of the bones may detect initial bony changes as early as three weeks following the surgical operation, while radiograms show them after about 4-6 weeks [13]. AP and lateral x-ray pictures are the most commonly performed, however, an important role of computed tomography is emphasized, which provides us additional information about the size, a precise location of the lesion and a possible proximity of the blood vessels. The most frequently scale used in the assessment of HO is Brooker's classification [12]. It is based on a radiographic assessment after total hip arthroplasty (THA) and contains 4 stages. Stage 1 and 2 are believed to be clinically insignificant, because they trigger symptoms very rarely. Stage 3 and 4 are considered to be clinically significant, as the complaints appear during their course. Another useful grading system is Alonso classification based on a computed tomography examination.

Alkaline phosphatase level was deemed to be a screening test for HO [13,14]. Its level exceeded the norm 2 weeks after the surgical procedure. Alkaline phosphatase levels usually exceed the norm 3 to 5 times within 10 weeks after an injury, and return to normal after 18 weeks [13]. Regrettably, alkaline phosphatase level is an unreliable predictor to assess the advancement and the risk of recurrence of HO [13,27]. However, due to a low cost of the test and its simplicity, the test is commonly applied to detect early stages of HO.

Recently, the role of the measurement of prostaglandin 2 (PGE-2) concentration in a 24-hour urine collection as a predictor of an early HO development is discussed. A sudden urge of PGE-2 excretion may point to the need of performing bone scintigraphy [28]. It seems that an early diagno-sis with type I collagen cross-linked C-telopeptide (CTX-1) may be useful because of a low cost and a fast prognostic evaluation [29]. Recently, the value of the measurement of PGE-2 concentration in a 24-hour urine collection has been reported as a good predictor in an early diagnosis of HO. A sudden increase of PGE-2 excretion may indicate the need for bone scintigraphy.

Prophylaxis

Non steroid anti inflammatory drugs

The prophylactic effect of NSAIDs administered after lower limb orthopaedic surgery is a commonly accepted prevention
of HO and is utilized to reduce the inflammatory process. In view of that, it belongs to the Basic Guidelines for Study Conduct [30,31]. NSAIDs act by prostaglandin-dependent inhibition, PGE-2 in particular, bone remodeling and via direct inhibition of the differentiation of osteoprogenitor cells [30]. A review study conducted by Cochrane Review involved 16 randomized clinical studies which had been assessing NSAIDs in the prophylaxis of HO [32]. The use of these drugs resulted in the risk reduction by 59% compared to the control group treated with a placebo. In another review paper by Neal et al. [33] the authors demonstrated a HO risk reduction by 57%. A statistical analysis of the paper assessed that a pre-operative administration of NSAIDs may prevent from 10,000 to 20,000 cases of pathologic bone formation out of every 100,000 total hip arthroplasty procedures performed in the United States. The analysis did not reveal an increase in gastrointestinal complaints during NSAID therapy.

An essential problem during the administration of high doses of indomethacin or other NSAIDs may be bone healing disturbances. Failures in bone healing, worse wound healing, including the ligament apparatus have also been found. One of the articles by Burd et al [34,35], reported 29% of cases of a failure in long bone healing during NSAID therapy compared to only 7% of patients who had undergone radiotherapy. Also of note are observations by Persson et al. [36], who analysed 142 patient with a fully developed HO after the THA. Among 11 cases of review surgeries due to aseptic loosening of endoprosthesis, 10 patients received indomethacin prophylaxis.

**Radiotherapy**

The studies of Cooley [37] in 1958 and later those by Craven and Urist [38] in 1971 revealed ionizing radiation effect on bone growth and repair. The observation of bone growth in rats proved that the radiation results were much better when the treatment was implemented within a short time after fracture. The authors hypothesised that the early osteoprogenitor cells which take part in bone growth were more radiosensitive than the more mature cells which were seen later. In 1981, Coventry et al. [39] introduced the use of radiotherapy as prophylactic treatment of HO by irradiating 42 patients who had undergone hip surgery. Each patient from the high risk group for HO formation received a dose of 20 Gray. Ectopic bone was developed in 19% of the patients. Recently, radiotherapy is utilized both pre- and post-operatively as the prevention of HO after bone fractures, “manipulation secondary to trauma” and surgical treatment [4]. The observation of Child et al. [40] was based on a retrospective cohort of 263 patients after traumatic acetabular fracture revealed HO only in 5.3% of patients who had undergone prophylactic irradiation, in contrast to 60% of patients who developed ectopic bone in some extent. Moreover, Chao et al. [41] noted that radiotherapy may lead to the prevention of HO in high-risk patients, in particular those who had a history of HO. Some authors noted that there is no significant difference between the situation when radiotherapy was used pre- or postoperatively [4].

The use of radiotherapy in prophylaxis carries a lot of potential risks. The most important is theoretical carcinogenesis; however, association between a neoplasm and radiotherapy in HO prophylaxis has not been proved [4]. It may be due to a low radiation dose and an advanced age of patients. The process of carcinogenesis following irradiation takes from 15 to 24 years, so it is possible that there are too few patients who have survived long enough to observe carcinogenesis [4]. Another adverse effect of radiotherapy is the risk of disorders of bone union process, observed during trochanteric osteotomy necessary to remove a prosthesis during revision surgeries [18]. Lack of bone union ranged between 12-30 % of patients who had received RT [4]. Lo et al. claim that 2 out of 4 patients undergone 2 out of 6 patients who had undergone osteotomy developed foetal growth disturbances [42]. Radiation affects also fertility. Experiments on animals showed reversible oligospermia at doses as low as 20-70 cGray and a permanent azoospermia at a dose of 120cGy [4].

**NLPZ + radioterapia**

Another possible HO prophylaxis is combining NSAIDs with radiotherapy [25]. Both Pakos et al. [43] and Piatek et al. [44] found combination therapy to be effective. In the study of Pakos et al., only one patient developed clinically significant HO among 54 patients, while an overall incidence of HO was 20.4%. In the trial of Piatek, only one patient out of 24 developed HO.

The combination of NSAIDs and radiotherapy is acknowledged to be the gold standard of HO prophylaxis.

**Treatment**

Pathological ossification may be found in up to 90% of patients who have underwent THA. In a majority of patients, the lesion remain symptom-free and are diagnosed incidentally [45]. Despite the fact that efficient prophylaxis remains the gold standard and surgical intervention should be considered as an ultimate solution to the problem, it is believed that as much as 25-27% of patients showing clinically significant HO ought to undergo a surgical procedure based on an individual characteristic of a patient, pain intensity and the degree of the limitation of the range of motion of the joint [46]. Surgical intervention should be postponed until the maturation process of the osseous tissue achieves a certain stage. To assess this stage, cyclic serum alkaline phosphatase measurement activity (ALP) (which should decrease until it reaches normal values) and the CTX-1 level.
are used. The measurement of CTX-1 level performed on day 5 after the surgery may be effectively used for the prognosis of HO after 3 months [47]. Cyclic SPECT/CT scans of bones can be also used for that purpose (in which the radioisotope uptake should systematically decrease) [26]. It is particularly important because in case of a surgical intervention when the lesions are immature, their recurrence or progression may occur. In case of THA, recommended waiting time is 6 months. Just for comparison, in case of heterotopic ossifications following spinal cord injuries the waiting time is 12 months, and in cases following central nervous system damage – 18 months [14].

Because of the mentioned risk of recurrence, the surgical procedure has to be combined with the administration of NSAIDs and radiotherapy in the post-operative period [4]. The most recommended drug from the group of NSAIDs as a secondary prophylaxis following a surgery in indomethacin [4]. As Ippolito et al. demonstrated that a factor increasing the post-operative risk of lesion recurrence is the disturbance of neuromuscular control [48]. A combination of surgical procedure with physiotherapeutic techniques and performing gentle exercise can also exert a positive therapeutic effect. It must be remembered that surgical intervention poses a serious risk of complications such as deep vein thrombosis, infections, decubitus, and a massive blood loss [4]. It has been believed for many years that surgical procedure is the only effective solution in patients who have developed post-operative HO, while radiotherapy does not have any therapeutic impact. In this respect, the reports which show that radiotherapy can be successfully utilized in such patients seem to be very interesting [49]. The study conducted by Morcos et al. found that in a group of patients who developed HO following THA procedure, 89% stopped the expansion of the lesions after radiotherapy within 6 or 12 weeks following the surgical procedure [49]. These results may suggest that radiotherapy could be an alternative to the surgical treatment in case of well-developed HO, being at the same time a less invasive method with a narrower spectrum of unwanted effects.

Proposal of the algorithm of procedure

In the light of the above considerations, the authors present a proposal on a diagnostic-therapeutic algorithm in case of HO in patients who had undergone hip arthroplasty.

1. In patients who are scheduled to have a primary hip arthroplasty, it is necessary to determine the risk factors of HO. The risk factors include: the male gender, Forestier disease (diffuse idiopathic skeletal hyperostosis), ankylosing spondylitis, previous hip osteotomy, previous hip orthopaedic surgeries, recent orthopaedic procedures following hip fractures [17,18,19]. If any of the mentioned risk factors are present, APL and CTX-1 levels should possibly be assessed on day 5 after the procedure. If the values of the parameters are elevated, a one-time radiotherapy should be applied with 6-8 Gray 5 hours before or until 72 hours after the procedure. Moreover, NSAIDs pharmacotherapy should be implemented for 6 weeks after the procedure. After 6 weeks, laboratory parameters (ALP) should be checked. Further ALP measurements are scheduled after 3 and 6 months following the procedure. If the values of the parameters are elevated, NSAIDs pharmacotherapy should be applied.

2. In the group of patients without HO risk factors, the surgical procedure is performed, only ALP is checked 3 and 6 months following the procedure. Then, if the parameters are elevated, NSAIDs pharmacotherapy is implemented.

3. In the case when hip arthroplasty is going to be performed on the contralateral side of the same patient in whom HO was detected, the scheduled procedure should be preceded by laboratory test-winning (ALP). Furthermore, radiotherapy with 6-8 Gray within 5 hours pre- and 72 hours post-operatively should be applied. Correspondingly, after the procedure NSAIDs are applied for 6 weeks. Three check-ups of lab parameters are established – 6 weeks, 3 months and 6 months after the procedure. If any abnormalities of the parameters are found, the decision on prolonged NSAIDs is taken.

4. In spite of prophylaxis, there is still a risk of developing HO following a hip arthroplasty. If HO stage 3 or 4 according to Broker classification develops, the patient should be classified for surgical operation of the removal of ossifications. Surgical treatment should be preceded by laboratory diagnostics with APL for the assessment of possible activity of ossifications. The ossifications may be active, increasing for at least 12 months following the primary surgery. Apart from standard x-ray diagnostics, computed tomography with 3-D transformations should be performed for a more precise evaluation of ossifications and angi-CT in case of suspicion of the great blood vessels compression. If there is vascular compression, their obliteration should be considered. In the peri-operative period – from 5 before the procedure until 72 hours after it – radiotherapy with 6-8 Gray is used with NSAIDs for 6 weeks following the procedure. Laboratory check-ups are recommended 6 weeks, 3 months and 6 months following the procedure. If the values of the parameters are ab-normal, the prolongation of the pharmacotherapy with NSAIDs is considered. The choice of NSAIDs must be based on the presence of cardiovascular, gastrointestinal and risk factors and the functions of the kidneys.

References

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