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The role of muscular trauma in the development of heterotopic ossification after hip surgery: An animal-model study in rats

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ABSTRACT

Background: Heterotopic ossification (HO), the formation of bone in soft tissues, is a frequent complication after surgery of the hip and the pelvis. Although the pathophysiological entities responsible for the formation of HO remain largely unclear, muscle trauma is alleged to play a central role in the pathogenic mechanisms underlying HO. However, for this observation, made by many surgeons for decades, no objective evidence has been provided yet.
Methods: Fifty male Wistar rats were subjected to surgery of the right hip. The femoral canal was reamed in three steps up to 2 mm. Animals formed 2 groups: in group 1 (25 animals) every effort was taken not to injure the muscles. In contrast, in the rats of group 2 (25 animals), an additional muscle lesion was created. Twelve weeks after surgery, the amount of heterotopic bone was assessed using micro-computed tomography, and classified using a modified Brooker classification system. A chi-square test was used to assess the statistical hypothesis comparing both groups.
Results: A significant higher amount of heterotopic bone was observed in animals that underwent additional muscular trauma.
Conclusion: According to our data, muscle trauma seems to play an important role in the development of HO after hip surgery. Hence, during surgery, particular care not to injure the surrounding muscular tissue should be taken.

Introduction

Heterotopic ossification (HO), defined as ectopic bone formation in soft tissues, mainly occurs after hip replacement surgery or pelvic fracture surgery. It is a serious complication causing pain and a reduced range of motion of the hip joint, often leading to impaired function and loss of quality of life [1,2]. The incidence of HO after hip surgery is most often reported to be around 20%, with a broad range of incidence of 16–90% [3–5]. Of these 20%, about 10% develop ossifications that are clinically relevant [6]. HO after hip surgery is usually classified using the Brooker classification system [7]. Here, 4 different categories are distinguished as follows: (1) small bony isles in the soft tissue around the hip joint; (2) bone spurs originating from the trochanter and pelvis with a gap >1 cm; (3) same as 2 with a gap <1 cm; (4) complete ankylosis of the hip joint. To prevent HO in high-risk cases, e.g. patients with concomitant brain injury or in patients with a history of HO after surgery, indomethacin, celecoxib, and radiation are generally accepted prophylactic options [1,8,9]. In contrast, therapeutic options are limited [10]. Currently, surgical resection combined with peri-operative radiation to reduce recurrence, is the most common treatment [11]. Although the pathophysiology of HO remains largely unclear, most investigators speculate that muscular-trauma may play an important role [12–15].

In 1949, Heinen et al. already regarded an injury sufficient to cause proliferative repair as a precondition for the formation of HO [13]. Brumback et al. agreed with this statement and suggested in addition that during intramedullary nailing every effort should be made to minimise muscle damage, because the resultant soft

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tissue response could stimulate the formation of heterotopic bone [14]. Data form the animal-experiments of Schneider et al. supported this commonly held intuitive belief, although without statistical significance [15].

The aim of the present study was to investigate the role of muscular trauma in a surgically induced animal model of HO.

Methods and materials

Animals

Fifty male Wistar rats (weight 269–360 g; Charles River, Cologne, Germany) were subjected to a standardised surgical intervention of their right hip [16]. They were housed in standard cages with a 12 h light-dark cycle at a constant temperature of 21 °C, with unlimited access to water and standard dry food pellets. Animal care and management, as well as the experimental setup, the surgical protocol and procedures, respectively, were approved by the local ethical committee (23-177-07/G 13-1-047). A licensed, experienced veterinarian supervised the animal care and surgery.

Surgical technique

A 1.5 cm incision was made over the greater trochanter, and a sharp dissection was carried down to the bone. The gluteus maximus muscle was split in the direction of its fibres. After exposing the trochanter, a 0.5 mm electric drill was used to open the femoral medullary canal just medially of the tip of the greater trochanter. The femoral canal was reamed by hand with incrementally larger reamers up until 2 mm. In 25 animals, an additional muscular trauma to the gluteus (maximus and medius) muscles was created by placing two Kocher clamps across the muscles forming a 0.5 cm equilateral triangle. Muscular injury was created for 3 min after femoral reaming (muscle trauma (MT) group). After removal of the clamps, the wound was closed in layers. In the 25 other animals efforts were made to protect the muscles (muscle protective (MP) group). Postoperative analgesia was provided by adding tramadol (0.5 mg/ml) to the drinking water; no anti-inflammatory agents were used. The rats were permitted to ambulate ad libitum.

μCT, classification and statistics

After 12 weeks, the animals were euthanised by CO_2 inhalation. The right hip with the proximal half of the femur and approximately half of the attaching pelvic bone including the surrounding soft tissue were resected and removed, fixed in paraformaldehyde, and subjected to micro-computed tomography (μCT) analysis using a μCT-40 scanner (Scanco Medical AG, Bassersdorf, Switzerland). Multiplanar reconstructions were calculated using OsiriX (Pixmeo SARL, Bernex, Switzerland) and used for further analysis using a modified Brooker classification system. A score of 0–5 was attributed to the observed heterotopic bone around the hip. Hereby, '0′ was scored in cases where no HO was observed. A score of '1′ was given when very small particles of heterotopic bone (all measuring under 1 mm) were found, a score of '2′ when particles of 1–2 mm were observed; '3′ was rated in specimens with bony particles greater than 2 mm, and a score of '4′ was given for near ankylosis (leaving less than 3 mm space between the two major fragments, i.e. trochanter – heterotopic bone and heterotopic bone – acetabulum). Finally, '5′ was given for complete ankylosis of the femur to the pelvis (Table 1). Statistical testing was done using the chi-square test with SPSS for macintosh (IBM, Armonk, New York, USA).

Table 1
Modified Brooker Score.

Modified Brooker Score (HO around the hip for rats)
1 All particles <1 mm
2 All particles <2 mm
3 Some particles >2 mm
4 Near ankylosis <3 mm between the three major fragments, i.e. trochanter – heterotopic bone and heterotopic bone – acetabulum
5 Complete ankylosis

Results

Forty-eight of 50 animals survived the procedure. Two animals died shortly after surgery; as both of them showed a very high respiratory rate, we may speculate that they died of pulmonary complications, e.g. pulmonary embolism. All other animals began to ambulate immediately after surgery and were able to return to normal mobility within 3 days.

μCT of the specimen showed no HO in one animal of the MT group and in 3 animals of the MP group. In all other animals, HO of different grades was seen (Fig. 1). Seventeen animals showed very small particles of HO, 11 animals were part of the MP group, 6 were part of the MT group (grade 1; Fig. 2). Thirteen animals showed HO particles of moderate size, 7 animals were part of the MP group and 6 were part of the MT group (grade 2; Fig. 3). Ten animals showed large particles of HO, 2 animals were part of the MP group and eight animals were part of the MT group (grade 3; Fig. 4). In 4 animals near ankylosis was observed, all were part of the MT group (grade 4; Fig. 5). No complete ankylosis was observed (grade 5).

A significant difference in distribution of the modified Brooker score was seen between the two groups ($p = 0.039$).

Discussion

The aim of the present investigation was to evaluate the role of muscle trauma for the development of heterotopic ossification after hip surgery. An animal model that mirrors the surgery in humans without exogenous osteogenic stimulus, was used as deliberately causing extra muscle trauma in humans cannot be considered ethical justifiable [17]. We were able to prove that muscular injury plays an important role in the development of HO after hip surgery. In our model, a significantly higher amount of HO at 12 weeks postoperatively could be demonstrated in the animals that were subjected to extra muscular injury during hip surgery.

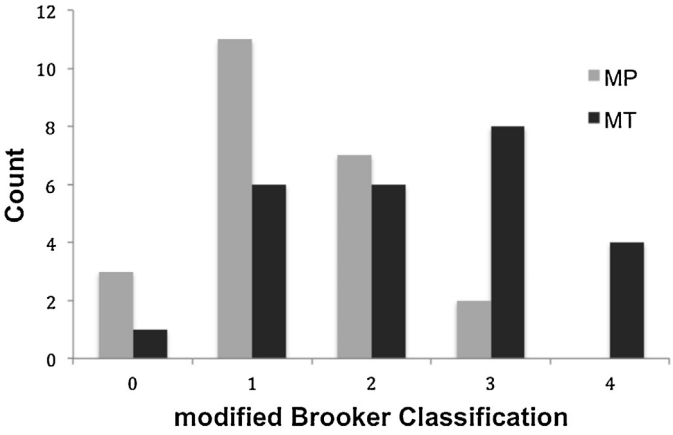

Fig. 1. Grades of HO in different animals: the modified Brooker grade of HO is shown on the *x*-axis and the number of animals is shown on the *y*-axis. The rats without additional muscular trauma (MP) are depicted in light grey, dark grey (MT) represents the group with additional muscle trauma.