Osteonecrosis after treatment for heterotopic ossification in spinal cord injury with the combination of surgery, irradiation, and an NSAID

AA van Kuijk^{*1}, HJM van Kuppevelt¹ and DB van der Schaaf²

¹Department of Rehabilitation, Sint Maartenskliniek Nijmegen, The Netherlands; ²Department of Orthopaedic Surgery, Sint Maartenskliniek Nijmegen, The Netherlands

Study design: Case report.

Objective: Heterotopic ossification (HO) is a frequent complication in spinal cord injury (SCI) that is often difficult to treat. Although surgery may become necessary, operative resection has been associated with complications and poor outcome due to a high recurrence rate. Additional methods of treatment to reduce the recurrence rate have been developed, including post operative irradiation and NSAIDs. This article presents three patients, who developed an osteonecrosis of the femoral head after the combined treatment for HO of surgery, irradiation, and an NSAID.

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Introduction

Heterotopic ossification (HO) is a frequent complication in spinal cord injury (SCI). The incidence in literature ranges from 10% to 53% depending on study design, the methods of detection, and the awareness of the disease.^{1–8} In 20% to 30% of spinal cord injured patients, clinically significant HO develops, most frequently at the hip.^{5,8–15} Reduction of hip joint movement may lead to loss of an adequate sitting position, pressure sores, increase of spasticity, and pain.⁹ These problems often require surgical resection of HO. However, operative resection of HO is often associated with severe complications and poor outcome. Complications include deep or superficial infection, post-operative haemorrhage, fractures, and a considerable recurrence rate. Different prophylactic treatment methods have been developed to reduce the recurrence rate, including diphosphonates, nonsteroidal antiinflammatory drugs (NSAID), and more recently irradiation. All methods seem to be successful in preventing HO after (elective) total hip arthroplasty. To date, no controlled studies are available about the effectiveness of these methods in spinal cord injured patients. We report three cases of osteonecrosis of the femoral head after surgical resection of heterotopic ossification with prophylactic post operative irradiation and an NSAID.

Case reports

A 30-year-old man sustained a C6 fracture resulting in C6-complete tetraplegia (ASIA A impairment scale)

following a motor-vehicle accident in October 1993. Ten months post injury, he developed a deep vein thrombosis in the iliac and femoral vein of the left leg, complicated by pulmonary embolism. Anti-coagulation therapy was complicated by retroperitoneal bleeding, and computerised tomography of the abdomen showed migration of blood into the quadriceps region of the left leg. Despite treatment, the left thigh remained red and swollen. Laboratory evaluation showed an increased serum alkaline phosphatase level, and the anteroposterior roentgenogram of the pelvis revealed a calcification in the quadriceps region. HO was diagnosed, and treatment with sodium etidronate 10 mg/kg/day was started for 12 weeks. The evolution of HO was monitored by serial anteroposterior roentgenograms of the pelvis and alkaline phosphatase levels. On serial roentgenograms an increase in HO was seen until January 1997. Alkaline phosphatase levels remained elevated until June 1997. Bone scans in December 1994 and April 1995, showed increased uptake of the HO. Range of motion of the hip joint decreased over time and 17 months after injury the hip became ankylosed with the resulting loss of an adequate sitting position. A technetium bone scan at that time showed no increased uptake, and the HO of the left hip was resected in June 1997. Preoperatively, a 3-D computerised tomography was made to define the exact configuration and extent of HO and its relationship to surrounding structures.^{9,16} Measurements of ROM in flexion and extension direction were made pre and post-operatively (Table 1). Surgery was performed under fluoroscopic control using a ventrolateral approach. Resection was performed until 90° of hip flexion could be obtained. Post-operative management

*Correspondence: AA van Kuijk, Sint Maartenskliniek, Department of Rehabilitation, PO BOX 9011, 6500 GM Nijmegen, The Netherlands

Table 1 Range of motion (ROM)

ROM	Patient 1	Patient 2	Patient 3
HO diagnosis	flex/ext 100°-0°-0°	flex/ext 95°-0°-10°	flex/ext 90°-0°-0°
Pre-operative	ankylosis in 8° flexion	ankylosis in 80° flexion	ankylosis in 90° flexion
Post-operative	flex/ext 100°-0°-0°	flex/ext 100°-0°-10°	flex/ext 110°-0°-0°

Figure 1 Postoperative AP of the pelvis demonstrating osteonecrosis of the right hip, with deformation of the collum femoris

included irradiation with 7 Gy in one session and indomethacin 25 mg three times daily for 6 weeks. Follow up roentgenograms made respectively 1 week, 6 weeks, and 3 months post-operatively, revealed no signs of fractures, or of HO recurrence. Incidental osteonecrosis of the femoral head was first seen 3 months after operation (Figure 1). Two years after surgery, adequate sitting position was preserved, as was ROM, and no increase of spasm or of pain have been noted.

The second patient concerns a 31-year-old man with a T7 complete paraplegia (ASIA A impairment scale) due to transverse myelitis in May 1995. Four months after disease onset, laboratory evaluation revealed an acute rise of the serum alkaline phosphatase level. Physical examination of the hip joint showed decreased range of motion. In addition, an anteroposterior roentgenogram of the pelvis indicated HO at the level of the great trochanter and the medial part of the femoral neck on the left side. Despite treatment with sodium etidronate (20 mg/kg/day for the first 2 weeks and 10 mg/kg/day for an additional 10 weeks), range of motion continued to decrease. As a result of the inadequate sitting position and increase in spasticity, a decubitus wound in the region of the left tuber ischiadicum developed. Alkaline phosphatase levels remained elevated until February 1997. By December 1997 the hip joint became clinically ankylotic and a corresponding technetium bone scan showed no increased uptake (Figure 2). A 3D-computerised

Figure 2 99m Technetium bone scan demonstrating heterotopic ossification about the left hip, os ileum and femur

tomography was made (Figure 3), and surgical resection of HO of the hip followed in February 1998. An identical operative and post-operative regime as described above for the first patient was used. Two months after operation, fever developed with an increase of spasm, and the patient was admitted to the hospital. A deep infection of the hip with osteonecrosis of the femoral head was diagnosed. No

Figure 3 3D-computerised tomography demonstrating the extent and configuration of the heterotopic ossification

signs of fracture were seen on follow up roentgenograms after surgery. Follow up until 1 year post-operative revealed no signs of HO recurrence, and an adequate sitting position as well as ROM, have been preserved.

The third patient presented concerns a 21-year-old man with T7 complete paraplegia (ASIA A impairment scale) due to a gunshot wound in December 1994. Two months after SCI, at the admission to our rehabilitation centre, a decreased range of motion of both hips was discovered on physical examination. Serum alkaline phosphatase was elevated, and the anteroposterior roentgenogram of the pelvis showed HO on both hips. Sodium etidronate (20 mg/kg/day for the first 2 weeks and 10 mg/kg/day for an additional 10 weeks) was given. Technetium bone scans showed increased uptake until May 1997, at that time a steady state in the ratio of uptake between normal and heterotopic bone was seen. In January 1998 the bone scan revealed again a steady state and the right hip was operated on HO 3 years after diagnosis. The patient underwent an identical operative and postoperative regime as the first two patients presented. Three months after operation, osteonecrosis of the femoral head was discovered on follow up anteroposterior roentgenogram of the pelvis. There were no signs of fracture or of HO recurrence, and an adequate sitting position was preserved, as was ROM.

Discussion

HO, a frequent complication in SCI, develops in 10% to 53% of all SCI patients. In 20%, HO leads to reduction in range of motion leading to loss of function, and in 5% ankylosis develops.^{1-7,9-12,14} HO develops below the level of injury, most commonly at the hip^{8,10-15,17} and usually along the anteromedial plane of the hip joint.^{5,9,11} Complete transverse SCI is more commonly associated with HO

than incomplete lesions.^{1,8,14,17} Other variables associated with HO formation are the presence of pressure sores and spasticity.⁹ Although it can develop even after several years, HO is generally diagnosed between 1 to 4 months post-injury with a peak incidence at 2 months.^{1,6,18}

The most common finding on clinical examination to indicate the presence of HO is a decreased range of motion, followed by a localised swelling.^{9,19} Erythema and warmth also occur. The early symptoms must be differentiated from osteoarthritis, thrombophlebitis, and tumour. An elevated serum alkaline phosphatase may be of value in differentiating early HO from other inflammations, as elevation of alkaline phosphatase levels precede the roentgenographic diagnosis. The usual interval is reported less than two weeks, but an interval of 4 months has been reported.⁷ Thus in the early stage of HO formation, the roentgenogram may be negative. Ultrasonography can be used in the early identification of clinically suspected HO and to differentiate HO from deep vein thrombosis, or a developing pressure sore, infection, or tumour.²⁰⁻²²

In the literature the evolution of HO is monitored by serial anteroposterior roentgenograms of the pelvis, by serum alkaline phosphatase levels, and/or by bone scintigrams. Although alkaline phosphatase levels are indices for active bone formation, normal levels do not predict maturity or recurrence, and alkaline phosphatase levels do not correlate with either peak activity or number of HO lesions.^{6,9,23} However, the roentgenographic appearance is not a reliable parameter for judging the maturity of HO,^{7,11} and it is an insensitive tool for predicting recurrence.²³ With a large block of ectopic bone interpretation of the roentgenogram is difficult, and immature elements may be obscured by mature bone.¹¹ The 99m technetium bone scan is the most sensitive tool in identifying HO and determining maturity.^{23,24} Serial decrease or a steady-state uptake ratio between normal and heterotopic bone is a reliable indicator for HO maturity.⁹ In the literature the occurrence of maturity of HO in SCI is reported at 12-18 months after first clinical presentation.^{5,10,18}

To date there is no satisfactory treatment to prevent HO occurrence. Once HO has been documented, patients can be treated with sodium etidronate, which to some extent has an inhibitory effect on the development of HO but which does not inhibit the formation of osteoid matrix. After diphosphonate treatment has been discontinued, HO continues to progress; the extent of recurrence varies in literature.^{4,14,25-27} Stover reported disodium to be potentially effective in preventing HO provided treatment was started before HO developed. The drug had minimal influence on HO already present, although the rate of progression may possibly have been slowed.²⁶ NSAIDs are used after total hip arthroplasty to prevent HO occurrence.^{27,28} The effect of NSAID has been attributed to inhibition of the inflammatory response or suppression of mesenchymal cell proliferation.⁹

The indication for surgery is improvement of hip motion to achieve adequate sitting and/or standing position, reduction of spasms and prevention of pressure sores.^{11,29,30} In the literature there is no consensus as to the most effective timing for the surgery. It has been suggested that recurrence of HO after resection is lessened if HO is removed during a radionuclide steady state.^{9–11,24,31} While Stover did not find any correlation between the extent of recurrence and length of onset of HO to surgery,²⁹ Freebourn stated that early resection of immature HO may not be predictive of a higher recurrence rate.³²

Because HO resection is associated with poor outcome mainly due to a high recurrence rate, different prophylactic methods have been developed to reduce the recurrence rate. Both irradiation and indomethacin seem to be effective in preventing HO occurrence after total hip replacement.^{27,28,33–36} However, the exact mechanism by which irradiation prevents HO development remains unknown. Irradiation may disrupt the differentiation process of pluripotential mesenchymal cells into osteoblasts.^{32,34} It may also serve to decrease pain perception associated with the tissue inflammatory reaction around the side of HO, or it may be involved in ablation of pain receptors.³⁴ Post-operative irradiation has been reported to decrease the recurrence of HO after surgical resection of HO in SCI, but no controlled studies are available.^{37–40} Sautter-Bihl *et al* treated 20 SCI patients with irradiation with 10 Gy in single fractions of 2 to 2.5 Gy. In 15 patients irradiation was performed as primary treatment to prevent HO formation, in seven patients it was used after operative HO resection to prevent HO recurrence. Four patients of the seven operated on, received a total hip prosthesis. In a follow up period of 12 weeks, none of the patients showed progression of HO. In five patients ROM and sitting position had decreased after 44 months. No radiographic control of the affected hip was performed.³⁸

Reported complications of radiation therapy include delayed wound and bone healing as well as the risk of developing a radiation induced sarcoma. The latter complication is not mentioned at radiation doses less than 30 Gy delivered within a 3-week period,^{41,42} however it limits the use of radiation therapy as the primary prevention of HO, when the patient's long life expectancy and the frequent involvement of multiple joints in spinal cord injured patients are taken into account.³⁹

Anti-inflammatory drugs inhibit the formation of prostaglandins and related substances which trigger the local bone remodelling, thereby reducing the formative and resorptive phases of bone remodelling.^{27,28,32} Both indomethacin and radiation therapy could exert their prophylactic effects by preventing the differentiation of the pluripotential mesenchymal cells into osteogenic cells.

Resection of HO is associated with severe complications, including excessive bleeding, deep or superficial

(wound) infection and fractures. In our series, all patients developed an osteonecrosis, a complication after surgery not previously mentioned in literature. While the exact aetiology and pathogenesis of osteonecrosis are still unknown, several conditions have been associated with osteonecrosis. These include fractures and dislocations of the hip, therapeutic irradiation, corticosteroid therapy, and the chronic use of anti-inflammatory as well as analgesic preparations.^{43,44}

Osteonecrosis is a well known, but infrequent complication of therapeutic pelvic irradiation. In the literature, two theories for the pathogenesis of radiation induced osteonecrosis exist. In the first theory, irradiated bone is proposed to be more susceptible to infection and trauma resulting from radiation induced vascular damage. After irradiation, fibrosis and intimal thickening of the small arterioles with luminal narrowing and obliteration of vessels in bone, synovium and surrounding capsular tissues have been reported.^{45–48} However, since the degree of this vascular impairment is insufficient to produce osteonecrosis, other factors such as trauma or infection must co-exist.⁴³

Another proposed mechanism for radiation induced osteonecrosis is the destruction of the bone cell population. After therapeutic irradiation, the most prominent change in bone is osteoporosis with histological evidence for decreased osteoblast and osteoclast activity, leading to disruption of the normal equilibrium of bone metabolism.^{45,48} However irradiation does not completely nor permanently suppress the osteoblastic activity. Hence, one must conclude that a combination of cell population destruction with other predisposing factors leads to osteonecrosis.^{45,48}

Furthermore, osteoporosis, in conjunction with the diminution of the normal and protective pain responses, could lead to osteonecrosis. In spinal cord injured patients, disuse osteoporosis is frequently observed below the level of SCI, and this is more pronounced at the hip.⁴⁹ Microfractures of subchondral bone occur in osteoporosis, which is more likely in states of diminished sensibility in particular if there is increased exposure to trauma.⁴³ Such microfractures could lead to cell death, and the subsequent subarticular collapse of the femoral head. In addition enzymatic products of cell death might induce a local inflammatory exudate, and thus mediate a progressive increase in pressure within a closed bony compartment. Such bone marrow pressure may directly affect local vascular resistance and bloodflow.⁴⁴ The end result of the above process is that the increased bone marrow pressure could impede the blood supply, leading to osteonecrosis.

In this study a combination of treatments were used: an operation, followed by irradiation, and the use of an anti-inflammatory drug. Although radiation was performed in one session and in a relatively minor dose compared to therapeutic radiation therapy, the combination of irradiation and the suspected pre-

existing osteoporosis may have led to osteonecrosis. It is also possible that during the operation damage to the vessels of the vascular system of the femur might have occurred. As mentioned above, such damage in bloodflow could lead to increased bone marrow pressure and predispose to osteonecrosis. However, the exact cause of osteonecrosis in our patients remains unknown.

Despite the osteonecrosis, adequate sitting position, which was the main reason to operate, was preserved, as was the range of motion of the hip joint. Up until now, the osteonecrosis does not seem to have produced any functional implications. Obviously the relatively short follow up period makes it impossible to predict any future implications of osteonecrosis.

In conclusion, although irradiation is known to be effective in the prevention of HO after total hip surgery, the three cases of femoral head osteonecrosis following a combined treatment of surgery, irradiation and an NSAID indicates that such a regime may not be appropriate for SCI patients. From our study the clinical implications of osteonecrosis appear minimal but are not completely understood at this time.

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