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Ⅳ. 研究成果の刊行物・別刷

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Patellar Fracture After Total Knee Arthroplasty for Rheumatoid Arthritis

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Abstract: Patellar fracture is one of the most challenging complications of total knee arthroplasty, but relatively, little is known about it in patients with rheumatoid arthritis. We retrospectively analyzed 329 total knee arthroplasties performed in 230 female patients with rheumatoid arthritis to identify the incidence and risk factors for postoperative patellar fractures. The mean age was 61.8 years, and the mean follow-up period was 6.2 years. Patellar resurfacing was performed in all cases. Five postoperative patellar fractures (1.51%) were identified, and a thin residual patellar thickness and the use of posterior-stabilizing components were identified as significant risk factors, although the number of fractures was small in both groups. There was also tendency of higher age and greater joint line change observed in patients with fracture compared with those without fracture. **Keywords:** patellar fracture, total knee arthroplasty, rheumatoid arthritis, postoperative complication, risk factor.

Total knee arthroplasty (TKA) is an effective treatment option relieving arthritic pain and restoring the function and activity of daily living in patients with osteoarthritis (OA) and rheumatoid arthritis (RA). Although patellar resurfacing is a common surgical procedure in TKA, it is sometimes associated with complications such as fracture, subluxation, component loosening, and patellar clunk syndrome. Patellar fractures are rare but also comprise one of the most challenging complications of TKA. Previous reports have provided valuable information concerning the prevalence and risk factors for postoperative patellar fractures. However, most of the studies have focused on patients with OA, and only a few studies analyzed patients with RA [1-3]. In the present study, we examined the incidence of patellar fractures in female patients with RA after TKA with patellar resurfacing, and analyzed the risk factors. We also discuss the treatment strategy and the outcome in these fracture cases.

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Materials and Methods

This is a retrospective study and was approved by the research ethics committee of our hospital. Three hundred twenty-nine TKAs, which had been performed in 230 female patients with RA between 1992 and 2009 at one hospital, were retrospectively analyzed. Patients with less than 1 year of follow-up or with infection were excluded. Surgeries were performed by 4 orthopedic surgeons. The mean age at the time of surgery was 61.8 years (range, 30-85 years), and the mean follow-up period after TKA was 6.2 years. One hundred twenty of the implants were NexGen (Zimmer, Warsaw, IN), 105 were Scorpio (Stryker), 61 were AGC (Biomet, Warsaw, IN), 42 were Maxim (Biomet), and 1 was Miller-Galante (Zimmer). Three hundred six cruciate-retaining (CR) prostheses and 23 posterior-stabilizing (PS) prostheses were used. Patellar resurfacing was performed in all cases, and all of the components were cemented.

The Insall-Salvati ratio was calculated by dividing the patellar length by the patellar tendon length, as seen in the postoperative lateral radiographs taken with a measure. The change in the vertical level of the femorotibial joint line (joint line change) was measured by comparing the preoperative and postoperative lateral radiographs as previously reported [4]. In brief, preoperative joint line represents the distance from the tibia tubercle to the tibia plateau, and postoperative joint line is measured from the tibia tubercle to the weight-bearing surface of the tibial prosthesis. Residual bone thickness of the patella (patellar thickness) was measured from outer surface to the bone-cut line in the

Table 1. Patients with Patellar Fracture After TKA

Case	Age (y)	Time to Fracture (mo)	Trauma	Fracture Type	Implant
1	67	26	Yes	II	NexGen CR
2	64	1	No	II	NexGen CR
3	69	8	No	II	Scorpio PS
4	77	2	No	II	Scorpio PS
5	68	60	No	III	Miller-Galante PS

postoperative radiographs. The data on the lateral retinacular release (ie, performed or not) were collected from the surgical records.

For the assessment of risk factors associated with patellar fractures, the baseline characteristics, intraoperative factors, and radiographic parameters were compared between patients with and without patellar fracture, using the χ^2 test for the categorical variables and nonpaired *t* tests for numerical variables. Univariate logistic regression models were used to test the association between patellar fracture and risk factors. Then, the receiver operating characteristic curves were used to determine the optimal cutoff values.

Multivariable models were used to adjust for age and confounding factors. All analyses used a 2-sided type I error rate of 0.05 as the threshold for statistical significance and were performed with the use of JMP software (version 8.0; SAS Institute, Cary, NC).

Results

Five postoperative patellar fractures (1.51%) were identified during the observation period (Table 1). The mean age of these patients was 69.0 years (range, 64-77 years) at the time of TKA. Three fractures were identified within a year of the surgery. Of the 5 fractures, 4 occurred without any traumatic episode, and 2 of them were unexpectedly diagnosed by routine radiographic assessment. Four fractures were classified as type II in the Ortiguera and Berry Classification system, and the other was type III. Three components were the PS type, and the other 2 were the CR type.

Table 2. Characteristics of Participants

Characteristic	Fracture (−)		Fracture (+)		*P*
Participants	324		5		
Age (y)	61.7	(10.8)	69.0	(4.8)	.13
Insall-Salvati ratio	0.98	(0.15)	1.1	(0.15)	.29
Joint line change (mm)	7.8	(4.3)	10.8	(1.9)	.13
Patellar thickness (mm)	12.2	(1.6)	10.4	(1.8)	.01
Lateral release	158	(48.8%)	2	(40.0%)	.7
Implant					
PS	20	(6.2%)	3	(60.0%)	<.001
CR	304	(93.8%)	2	(40.0%)	

Data are expressed as mean (SD) or number of patients (%).

For the assessment of factors associated with patellar fracture, the baseline characteristics, intraoperative factors, and radiographic parameters were compared between the patients with and without a patellar fracture (Table 2). Patellar thickness was significantly lower in the group with than without fracture (mean, 10.4 vs 12.2 mm; $P = .01$), and the proportion with PS was significantly higher in the group with fracture ($P < .001$). Using the receiver operating characteristic curve, we determined that the cutoff point for the patellar thickness was 11 mm (area under the curve, 0.78; sensitivity, 80.0%; specificity, 67.9%). There was tendency of higher age (mean, 69.0 vs 61.7 years; $P = .13$) and greater joint line change (mean, 10.8 vs 7.8 mm; $P = .13$) in the fracture group. There was no tendency that 1 specific surgeon used specific type of prosthesis nor had higher prevalence of patellar fracture.

We constructed a multivariate logistic regression model to examine the correlation of the incidence of patellar fracture with patellar thickness and the use of PS components after adjusting for age and found that both patellar thickness and the use of the PS prosthesis were positively associated with the incidence of patellar fracture (Table 3).

We then reviewed the outcome of the fracture cases (Table 4). One type III fracture case was treated surgically by retrieving the patellar component, and the others were treated conservatively by applying knee braces for 2 to 3 weeks. No surgical procedures were performed in these cases. At the time of the latest follow-up, bone union was not observed in any of the cases, but all 5 patients reported that they had no pain and were ambulant; 2 of them used canes, and 3 did not. Extensor lag was less than 10° in all of the cases.

Discussion

Total knee arthroplasty with patellar resurfacing is generally favored in patients with RA [5-8], but we must be aware of the risk of postoperative patellar fracture. The reported prevalence of patellar fracture after TKA with patellar resurfacing ranges from 0.12% to 3.9%, which is higher than TKA without patellar resurfacing [3,9-12]. Little is known about patients with RA, but Grace and Sim [3] reported the incidence was 0.12% in patients with RA and 0.18% in patients with OA, with no significant difference between them. Scott et al [11] reported the incidence of postoperative patellar fracture

Table 3. Multivariate Logistic Regression Analysis for Odds Ratio and 95% Confidence Interval of the Risk Factors for Patellar Fracture

	Odds Ratio for Pain	95% CI	*P*
Implant: PS (vs CR)	30.30	3.85-311.68	.002
Patellar thickness	1.60	1.00-2.89	.049

Data were calculated by logistic regression analysis after adjustment for age and confounding. Abbreviation: CI, confidence interval.

Table 4. Treatment and Outcome in Each Fracture Case

Case	Treatment	Follow-Up (y)	Range of Motion (°)		Extensor Lag (°)	Bone Union	Pain	Walking Aid
			Before fracture	After fracture				
1	Knee brace	4	0-95	0-120	0	No	None	None
2	Knee brace	6	0-90	0-110	0	No	None	None
3	Knee brace	4	0-95	10-100	10	No	None	Cane
4	Knee brace	6	0-110	5-125	5	No	None	Cane
5	Patellar implant retrieval	10	0-90	0-90	0	No	None	None

to be 0.7% in patients with RA and 3.5% in patients with OA, suggesting a lower fracture risk in patients with RA. In our series, the prevalence of patellar fracture after TKA in female patients with RA was 1.5% (5/329 knees), which was within the range of the reported prevalence among the combined groups of patients with OA and RA.

Previous studies have reported risk factors for patellar fracture after TKA [13-15]. These include patient factors (RA, male sex, and osteoporosis), technical factors (excessive resection of patellar bone, lateral retinacular release, and revision surgery), and implant factors (PS type prosthesis, central peg, and cementless fixation). In the current study limiting the subjects to female RA patients with primary TKA, thinner postoperative patellar thickness and the use of a PS type of prosthesis were independently and significantly associated with patellar fracture. In addition, 4 (80%) of 5 fracture cases in our series occurred without a traumatic event. These findings imply that the increased patellofemoral contact stress, which results from using the PS type of prosthesis, and the reduced mechanical strength of the patella due to an excessive resection of the bone lead to stress fracture of the patella. However, we have to consider that there still have been an error of measurement using radiographs and that PS component could be preferred for patients with relatively severe deformity, which might have affected our result. In addition, it is possible that the higher frequency of patellar fractures in PS type of prosthesis is specific for the Japanese patients with a relatively wide intercondylar notch relative to the medial-lateral width of the femur.

In addition to these factors, there was a tendency of higher age and joint line change in the group with fracture. Excessive joint line change may exert an effect on the tibial-patellofemoral mechanical axis and increase the stress on the patella, as in the report by Figgie et al [4], where they found that an excessive joint line change (>8 mm) in TKA was associated with poor clinical results.

Ortiguera and Berry [10] proposed a classification system for postoperative patellar fracture. Using this system, in our series, 4 fractures (80%) were type II (implant intact/extensor mechanism disrupted), and 1 was type III (implant loose). In previous reports, type II fractures were relatively rare (15%-22%) [9,10,16], which is different from our cases. Therefore, our findings might reflect a special characteristic of female patients with RA.

The choice of treatment strategy for patellar fractures after TKA is controversial, but previous reports have tended to favor conservative treatment because of the considerable possibility of nonunion and infection after operative treatment [9,10,16,17]. Chalidis et al [17], in a systematic review, indicated that the mean nonunion rate after internal fixation with a tension-band technique or cerclage wire was 92%, with poor results in most cases. We treated 4 type II fractures nonoperatively with a knee brace for 2 to 3 weeks, and 1 type III fracture was treated operatively by retrieving the patellar component. Bone union was not observed in any case, yet all of these patients were ambulant, without reported pain, and exhibited only limited extensor lag (<10°) at the time of the last follow-up. Our clinical experience supports nonoperative treatment option.

In summary, we have described the prevalence, risk factors, and outcome of patellar fractures after primary TKA with patellar resurfacing in female patients with RA. Our analysis suggests that the residual bony thickness of the patella should not be less than 11 mm and that PS-type prostheses should be avoided if possible, especially in patients with a thin patella. In the event that a fracture does occur, conservative treatment seems a favorable choice.

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EDITORIAL

Regulation of bone destruction in rheumatoid arthritis through RANKL-RANK pathways

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Abstract

Recent studies have demonstrated that osteoclasts, the primary cells responsible for bone resorption, are mainly involved in bone and joint destruction in rheumatoid arthritis (RA) patients. Recent progress in bone cell biology has revealed the molecular mechanism of osteoclast differentiation and bone resorption by mature osteoclasts. We highlight here the potential role of the receptor activator of nuclear factor κB ligand (RANKL)-RANK pathways in bone destruction in RA and review recent clinical trials treating RA by targeting RANKL.

Key words: Rheumatoid arthritis; Osteoclast; Receptor activator of nuclear factor κB ligand; Bisphosphonate; Denosumab

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by remarkable synovial hyperplasia followed by the massive joint destruction[1,2]. Investigation into the pathogenesis of joint destruction in RA has revealed the transformed phenotype of rheumatoid synovial cells[3]. Proliferating inflammatory synovial cells lead to pannus formation that invades articular cartilage and bone[4]. Radiographic studies demonstrate that bone erosion in RA begins early in the disease, and progresses throughout its course[5,6]. Bone erosion results in severe deformity of the affected joints and impairs the normal activity of patients. Therefore, inhibiting bone destruction is one of the most challenging goals in the treatment of RA. Because the exact etiology of RA remains unknown, most treatments of RA have targeted symptoms of the disease. Non-steroidal anti-inflammatory drugs have been used to reduce the painful symptoms of the disease, but they have little effect on stopping the progression of joint destruction. Some disease-modifying anti-rheumatic drugs such as methotrexate are known to suppress joint destruction in RA[7,8]. In addition, recent clinical studies have demonstrated that various biological agents such as antibodies against inflammatory cytokines (e.g., infliximab, adalimumab and tocilizumab) or CTLA4-Ig (abatacept) not only suppress joint symptoms in RA patients but also markedly ameliorate joint destruction[9-12]. However, the bone-protective function of these drugs is still limited, and they are accompanied by severe side effects, such as infection, since they suppress a patient's immunological reaction[13].

There is accumulating evidence that osteoclasts, primary cells responsible for bone resorption, are involved in bone destruction in RA, and recent progress in molecular biology and biochemistry has revealed the molecular mechanism of osteoclast differentiation and bone resorption. In this chapter, I would like to focus on the role of osteoclasts in bone and joint destruction in RA, the mechanism of osteoclast generation in inflammatory joint, and propose that osteoclasts can be potential targets in RA therapy.

INVOLVEMENT OF OSTEOCLASTS IN BONE DESTRUCTION IN RA

RA is characterized by proliferative pannus formation leading to erosive bone destruction originating from the interface of cartilage and bone (the bare area). Synovial tissues of RA joints produce various inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which are believed to play important roles in joint destruction. The cellular mechanism of bone and cartilage destruction in RA still remains unclear, but recent studies have revealed the essential role of osteoclasts (Figure 1). Bromley *et al*[14] observed a number of acid phosphatase-positive multinucleated cells (chondroclasts and osteoclasts) in the erosive areas of RA joints obtained at the time of joint replacements. In collagen-induced arthritis, multinucleated giant cells were observed at the bone-pannus junctions of arthritic joints, and cells isolated from the lesions were able to differentiate into mature osteoclasts. Gravallese *et al*[15] also found multinucleated cells present on subchondral bone surface and in the areas of direct invasion of pannus into subchondral bone. Their important discovery was that those multinucleated cells were positive for unique markers of osteoclasts such as tartrate-resistant acid phosphatase (TRAP), cathepsin K, and calcitonin receptors, satisfying the major criteria of mature osteoclasts. Interestingly, some multinucleated cells and mononuclear cells apart from the bone surface were TRAP-positive. These findings suggest the possible role of synovial tissues for osteoclastogenesis in RA. To reveal the osteoclastogenic potential of RA synovial tissues, synovial cells from RA synovia were cultured in the presence of osteotropic factors such as 1β,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] and macrophage colony-stimulating factor (M-CSF)[16]. After 3 wk of culture, we observed many multinucleated giant cells, which were TRAP-positive, possessed abundant calcitonin receptors, and made resorption pits on dentine slices. We also demonstrated that peripheral monocytes can differentiate into osteoclast-like cells when co-cultured with synovial fibroblasts obtained from RA synovial tissues in the presence of 1,25$(OH)_2D_3$ and M-CSF. Similar results were reported by Fujikawa *et al*[17]. They found that synovial macrophages isolated from RA synovial tissues can differentiate into osteoclast-like cells when co-cultured with UMR 106 rat osteoblast-like cells. These results suggest that RA synovial fibroblasts can support osteoclast differentiation from monocyte-macrophage lineage precursor cells under a suitable condition, at least *in vitro*.

INVOLVEMENT OF RANKL/RANK PATHWAYS IN BONE DESTRUCTION IN RA

Remarkable progress has been made in recent years in the field of osteoclast research primarily due to the finding of the receptor activator of nuclear factor κB (NF-κB) ligand (RANKL)/RANK system[18]. RANKL is a member of the TNF superfamily of cytokines, which was originally identified as a membrane-bound survival factor for dendritic cells produced by activated T cells[19]. The expression of RANKL can be also induced in osteoblasts and bone marrow stromal cells by osteotropic hormones such as 1,25$(OH)_2D_3$ and parathyroid hormone[20]. In the presence of M-CSF, RANKL can stimulate osteoclast differentiation from hematopoietic precursor cells *in vitro*[20]. RANKL also acts on mature osteoclasts and activates the bone-resorbing activity and survival of the cells. RANKL binds to its receptor RANK, a transmembrane receptor belonging to the TNF receptor superfamily, which is expressed in monocyte-macrophage lineage osteoclast precursor cells as well as in mature osteoclasts and dendritic cells. Binding of RANKL to RANK induces intracellular signals including NF-κB activation and c-Jun N-terminus kinase activation. The other important actor in this system is osteoprotegerin (OPG) a soluble receptor of RANKL, belonging to the TNF receptor superfamily[19]. OPG specifically binds to RANKL, and inhibits RANKL activity by preventing its binding to RANK.

The essential role of RANKL/RANK signaling pathways in osteoclast development *in vivo* has been established by a series of targeted gene disruption experiments[19] comprising, the targeted disruption of either RANKL or RANK induced osteopetrosis in mice, a pathological bone disease which is characterized by an increased bone mass due to a deficiency in osteoclast differentiation[21,22]. We and another group found that mice deficient in TRAF6, a signaling molecule involved in RANK signaling, also showed osteopetrotic phenotypes. In contrast, the targeted disruption of OPG induces reduced bone mass in mice, reminiscent of osteoporosis, due to the increased number and activity of osteoclasts[18,23,24]. These results clearly demonstrate the essential role of RANKL/RANK pathways in osteoclast development and activation *in vivo*. The next question is whether the RANKL/RANK system is also involved in pathological bone destruction, such as in RA. We and others have revealed by Northern blotting, immunocytochemistry and *in situ* hybridization (Figure 2) that RANKL is highly expressed in synovial fibroblasts[12,15,25,26]. 1,25$(OH)_2D_3$ treatment increased the expression of RANKL in synovial fibroblasts and reduced the expression of OPG in the cells. RANKL expression was also detected in $CD4^+$ T lymphocytes in RA synovial tissues by *in situ* hybridization. Kong *et al*[27] demonstrated that activated $CD4^+$ T lymphocytes fixed with paraformaldehyde or culture supernatants from activated T cells can support osteoclast differentiation through the surface-bound and/or soluble RANKL they produce. They also showed that RANKL was expressed on the surface of activated T cells in synovial tissues of adjuvant arthritis rats[27]. These results suggest the important role of activated T lymphocytes in bone and joint destruction in RA. However, the role of T cells in osteoclast development is

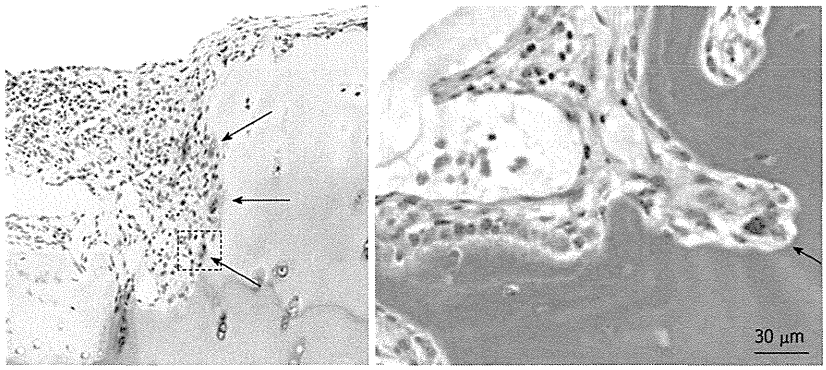

Figure 1 Inflammatory synovial proliferation and bone erosion (arrows) by osteoclasts in rheumatoid arthritis patients.

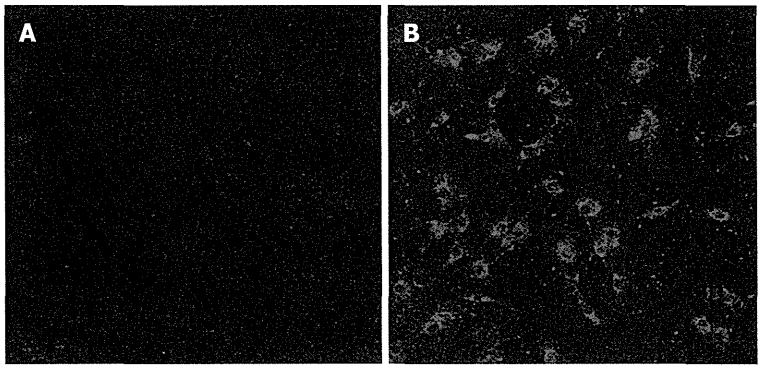

Figure 2 Immunostaining of synovial fibroblasts obtained from osteoarthritis (A) and rheumatoid arthritis (B) patients with anti-receptor activator of nuclear factor κB ligand antibody.

still controversial because activated T cells also produce many cytokines which inhibit osteoclast differentiation, such as interferon-β and IL-10. In any case, these studies indicate that RANKL produced by synovial fibroblasts and/or activated T lymphocytes in RA synovial tissues may play an essential role in osteoclast development and bone destruction in RA. Based on these findings, Kong *et al*[27] proposed that OPG can be a potent therapeutic agent against bone destruction in RA. Exogenous administration of recombinant OPG suppressed bone and joint destruction in rat adjuvant arthritis.

Reduced bone destruction in a patient with osteopetrosis and RA

In addition to the animal studies described above, the importance of osteoclasts in bone destruction in RA was further confirmed by the clinical finding in a RA patient with osteopetrosis[28]. Osteopetrosis is an inherited disorder characterized by an increase in bone mass[29]. In humans, osteopetrosis comprises a heterogeneous group of diseases, which are classified into three major groups on the basis of inheritance, age of onset, severity, and secondary clinical features: autosomal recessive infantile malignant osteopetrosis, autosomal recessive intermediate mild osteopetrosis, and autosomal dominant adult onset benign osteopetrosis. The most frequent form of osteopetrosis, which has autosomal dominant (ADO) inheritance (incidence 5:100000), is also called Albers-Schönberg disease or ADO type Ⅱ. ADO type Ⅱ is characterized by vertebral endplate thickening (rugger-jersey appearance), fragile bones with multiple fractures and delayed healing. Recent studies have shown that the *CLCN7* gene encoding type 7 chloride channel, which is essential for the acidification of the extracellular environment in resorption lacuna by osteoclasts, is a candidate gene for ADO type Ⅱ. We recently reported a very rare case of RA associated with ADO type Ⅱ. In spite of the severe inflammation and rapid progression of cartilage destruction in the patient, the progression of bone erosion was quite slow (Figure 3)[28]. These clinical findings further confirm the critical role of osteoclasts in bone destruction in RA but not in inflammation or cartilage destruction.

The mechanisms of action of aminobisphosphonate

Since osteoclasts are critically involved in bone destruction in RA, therapeutics which target osteoclasts could be good candidates for the treatment of RA. One of the most promising group of reagents which inhibit osteoclast function is bisphosphonates. Bisphosphonates (BPs), stable analogs of pyrophosphate, strongly inhibit bone resorption and have been used to treat various diseases driven by increased bone resorption, such as postmenopausal osteoporosis. Although BPs are poorly absorbed

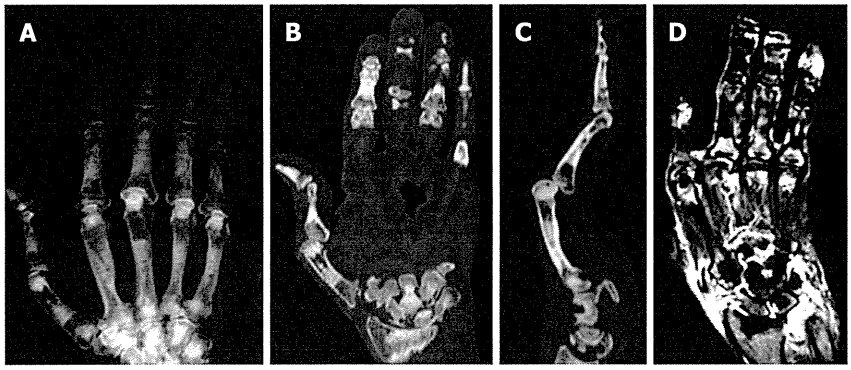

Figure 3 Plain X ray (A), computed tomography scan (B and C) and magnetic resonance imaging (D) of the right hand of an autosomal dominant II patient with rheumatoid arthritis. Erosion of the carpal bones (B) and severe synovitis, as determined by the high intensity areas by T2-weighted magnetic resonance imaging images (D), were observed[14].

from the intestine, they are quickly deposited on the bone surface once absorbed. BPs are divided into two groups according to the structure of the side chains, a nitrogen-containing type (N-BPs) and a non-nitrogen-containing type. Non-nitrogen-containing BPs are reported to act through the intracellular accumulation of non-hydrolyzable ATP analogs that exert cytotoxic effects on OCs, while N-BPs inhibit the mevalonate pathway and prevent the post-translational prenylation of small GTP-binding proteins such as Ras, Rho, Rac and Cdc42. We recently reported that risedronate, one of the N-BPs, induced osteoclast apoptosis by suppressing the Erk pathway and increasing the expression of a pro-apoptotic Bcl family protein, Bim, while it reduced bone-resorbing activity of the cells through suppression of the Akt pathway[30].

Osteoporosis and osteoporosis-related fractures are common in RA patients[31-33] and several studies have demonstrated that bisphosphonates effectively increase bone mineral density and decrease fragile fractures in RA patients[34-36]. In spite of these strong and specific inhibitory effects of bisphosphonates on osteoclasts, only limited clinical data demonstrate the effectiveness of bisphosphonates in RA patients. Jarette *et al*[37] reported preliminary evidence that treatment with zoledronic acid plus methotrexate showed better results in reducing bone destruction than methotrexate alone. However, many other studies have failed to show positive effects of bisphosphonates against bone destruction in RA[38-40]. This may be because, in these studies, the treatment was initiated too late or the strength of the bisphosphonates used was not enough to treat the bone destruction in RA.

Effects of anti-RANKL antibody on bone destruction in RA

Denosumab is a fully human monoclonal antibody that specifically and avidly binds to RANKL. Previous clinical studies have demonstrated that administration 60 mg of denosumab subcutaneously every 6 mo to postmenopausal women with osteoporosis significantly reduced bone turnover markers, increased bone mineral density, and reduced osteoporosis-related fractures[41]. Because of the critical role of the RANKL-RANK system in osteoclast development and bone destruction in RA, clinical studies were conducted to analyze the effect of denosumab on RA[42-44]. Sharp *et al*[42] demonstrated that twice-yearly subcutaneous injections of denosumab (60 mg or 180 mg) with ongoing methotrexate treatment significantly reduced cortical bone loss in RA patients for up to 12 mo. In a phase II clinical trial, subcutaneous administration of denosumab every 6 mo to patients with active RA suppressed the progression of subchondral bone erosions and systemic bone loss, although there was no an apparent reduction of joint inflammation or joint space narrowing. In addition, denosumab treatment over 12 mo increased mean lumbar spine and hip bone mineral density and reduced bone turnover markers such as sCTx-I and P1NP compared with placebo, regardless of baseline bone mineral density or marker levels or concomitant bisphosphonate or glucocorticoid use[44]. The rate of adverse events and serious infections requiring hospitalization did not differ between patients treated with denosumab and with placebo. These clinical observations, in addition to the results of the basic studies, clearly suggest that denosumab is effective in preventing bone erosion but not cartilage destruction in RA.

CONCLUSION

The ultimate goal of the treatment of RA is to prevent the bone and joint destruction and preserve the daily activity of patients. Recent studies have revealed that osteoclasts are involved in the pathogenesis of bone and joint destruction in RA and can be a potent therapeutic target of the disease[4,45]. Therapeutics targeting osteoclast formation or function can at least ameliorate the progression of these bone changes[27,43]. However, inhibition of osteoclast function by anti-resorptive agents alone do not completely prevent bone erosion in RA in spite of their preventive effects against systemic bone loss. Therefore, the combination of anti-resorption therapy and anti-inflammatory therapy could be an ideal therapy for RA. Thus, anti-RANKL therapy in combination with the

anti-inflammatory therapy is a promising strategy for RA treatment, and safe and effective therapies against RA may be expected in the near future.

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OPEN ACCESS

Mortality and morbidity after high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury: a propensity-matched analysis using a nationwide administrative database

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ABSTRACT

Objective To examine the magnitude of the adverse impact of high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury (SCI).

Methods We examined the abstracted data from the Japanese Diagnosis Procedure Combination database, and included patients with ICD-10 code S141 who were admitted on an emergency basis between 1 July and 31 December in 2007–2009. The investigation evaluated the patients' sex, age, comorbidities, Japan Coma Scale, hospital volume and the amount of methylprednisolone administered. One-to-one propensity-score matching between high-dose methylprednisolone group (>5000 mg) and control group was performed to compare the rates of in-hospital death and major complications (sepsis; pneumonia; urinary tract infection; gastrointestinal ulcer/bleeding; and pulmonary embolism).

Results We identified 3508 cervical SCI patients (2652 men and 856 women; mean age, 60.8±18.7 years) including 824 (23.5%) patients who received high-dose methylprednisolone. A propensity-matched analysis with 824 pairs of patients showed a significant increase in the occurrence of gastrointestinal ulcer/bleeding (68/812 vs 31/812; p<0.001) in the high-dose methylprednisolone group. Overall, the high-dose methylprednisolone group demonstrated a significantly higher risk of complications (144/812 vs 96/812;OR, 1.66; 95% CI 1.23 to 2.24; p=0.001) than the control group. There was no significant difference in in-hospital mortality between the high-dose methylprednisolone group and the control group (p=0.884).

Conclusions Patients receiving high-dose methylprednisolone had a significantly increased risk of major complications, in particular, gastrointestinal ulcer/bleeding. However, high-dose methylprednisolone treatment was not associated with any increase in mortality.

INTRODUCTION

Methylprednisolone is one of the most investigated agents for its neuroprotective potential, and remains the only drug used worldwide for acute spinal cord injury (SCI). The beneficial effect of high-dose methylprednisolone was initially reported in a series of National Acute Spinal Cord Injury Studies (NASCIS) in the 1990s.[1 2] Specifically, NASCIS-2 compared 24 h of high-dose methylprednisolone (given as a bolus of 30 mg/kg over 15 min followed by a continuous infusion of 5.4 mg/kg/h) with placebo in acute SCI patients.[1] Patients receiving methylprednisolone within 8 h of injury were reported to have greater neurologic improvement at 6 months. Results of NASCIS-3 further indicated slightly more recovery following 48 h of treatment than after 24 h.[2] Following publication of the NASCIS trials, the regimen of these trials was rapidly adopted worldwide; however, subsequent debate over the efficacy and safety of high-dose methylprednisolone treatment[3–5] has led to serious differences of opinion in the medical community, and considerable variations in current practice.[6–9]

According to a recent Cochrane review,[10] NASCIS-2 showed a weak trend towards an increase in complications, including wound infection (OR 2.11; 95% CI 0.81 to 5.49) and gastrointestinal haemorrhage (OR 1.48; 95% CI 0.48 to 4.56). The high-dose methylprednisolone group showed slightly lower 180-day mortality than the control group (7/162 vs 12/171; OR 0.62 95% CI 0.25 to 1.53). On the other hand, NASCIS-3, comparing 24 h and 48 h methylprednisolone administration, found a trend towards increased rates of severe pneumonia (OR 2.25; 95% CI 0.71 to 7.15) and sepsis (OR 4.00; 95% CI 0.45 to 35.38) in the 48 h treatment group. Mortality was not significantly different between the two groups.

Although many studies following the NASCIS trials reported a trend toward increased complications after high-dose methylprednisolone treatment,[11–15] the magnitude of its negative impact remains unclear. The reported incidence of complications after high-dose methylprednisolone administration varied greatly between studies, primarily because of small sample sizes and bias in selection of the study population. In addition, it is unknown whether high-dose methylprednisolone negatively affects the survival of SCI patients. Despite widespread use of this treatment, information from high-level evidence about the risks associated with high-dose methylprednisolone administration is lacking. We therefore conducted a retrospective observational study based on a propensity score-matched analysis of data from a nationwide administrative database to examine the risk of high-dose methylprednisolone treatment after acute cervical SCI.

METHODS

Diagnosis Procedure Combination database

The Diagnosis Procedure Combination (DPC) is a case-mix patient classification system which was

launched in 2002 by the Ministry of Health, Labour and Welfare of Japan, and was linked with a lump-sum payment system.[16] All 82 university teaching hospitals are obliged to adopt this system, but adoption by community hospitals is voluntary. The survey in the participating hospitals is conducted between 1 July and 31 December each year by the DPC research group, in collaboration with the Ministry of Health, Labour and Welfare. In 2009, the number of participating hospitals was 818 and the number of patients included was 2.57 million, which represented approximately 40% of all inpatient admissions to acute care hospitals in Japan. The database includes administrative claims data and the following data: unique identifiers of hospitals; patient age and sex; diagnoses, comorbidities at admission and complications after admission recorded with text data in the Japanese language and the International Classification of Diseases, 10th Revision (ICD-10) codes; consciousness level at admission measured with the Japan Coma Scale (JCS; see Appendix); discharge status; and drugs administered.[17] In the DPC database, complications that occur after admission are clearly differentiated from comorbidities that already present at admission. To optimise the accuracy of the recorded diagnoses, physicians in charge are obliged to record the diagnoses with reference to medical charts. Because of the anonymous nature of the data, informed consent was waived when this study was approved by the institutional review board at The University of Tokyo.

Patient selection and data

Using the DPC database, we identified patients who had an emergency admission to the participating hospitals with a diagnosis of cervical SCI (ICD-10 code, S141) between July and December, 2007–2009. Patients who were transferred from other hospitals were excluded. Although we were unable to confirm the presence of a neurological deficit in each patient, miscoding is relatively unlikely because the DPC data are coded by physicians and subjected to an audit. The list of drugs used during hospitalisation was reviewed for each patient, and we identified patients who started high-dose methylprednisolone treatment for acute cervical SCI at admission and received a total of ≥5000 mg methylprednisolone infusion. In Japan, many elderly patients who sustain a cervical SCI are lean. For a 40 kg person, the total dosage amounted to 6168 mg in the NASCIS-2 protocol. Therefore, we set a cut-off value of 5000 mg. As a control group, we identified cervical SCI patients who did not receive methylprednisolone, or those who received less than 500 mg methylprednisolone during hospitalisation. We selected this cut-off value according to the definition of 'high-dose' adopted by Sauerland *et al*[18] (>15 mg/kg (600 mg for a 40 kg person) or >1000 mg).

We assessed patient background, including age, sex, JCS score and Charlson Comorbidity Index (CCI). JCS 0 indicates patients with alert consciousness; JCS one-digit codes (1–3) indicate patients who are drowsy but awake without any stimuli; JCS two-digit codes (10–30) indicate patients with somnolence who can be aroused with some stimuli; JCS three-digit codes (100–300) indicate coma.[19] The JCS and the Glasgow Coma Scale assessments are well correlated. The CCI is a prognostic index as a means for quantifying the prognosis of patients enrolled in a large cohort, and is used widely to measure the case-mix with administrative data. This index is based on a point scoring system (from 0 to 40) for the presence of specific associated diseases. Quan *et al*[20] provided a validated chart showing how each comorbidity corresponds to a set of ICD-10 codes.[20] Based on Quan's protocol, each ICD-10 code of comorbidity was converted into a score, and was summed for each patient to determine CCI. Hospital volume was defined as the annual number of patients with cervical SCI at each hospital.

Clinical outcomes included in-hospital deaths and major complications (sepsis (ICD-10 codes: A40, A41), respiratory complications (pneumonia (J12-J18), postprocedural respiratory disorders (J95) or respiratory failure (J96)), pulmonary embolism (I26), gastroduodenal ulcer/bleeding (K25, K26), urinary tract infection (N10, N30, N390)).

Statistical analyses

We performed a one-to-one matching of patients in the high-dose methylprednisolone group and the control group on the basis of estimated propensity scores of each patient.[21] The propensity-score approach addresses selection bias that is inherent in retrospective observational studies, where outcomes can reflect a lack of comparability in treatment groups rather than the effects of treatment. This approach tries to construct a randomised experimental-like situation where treatment groups being contrasted are comparable for observing prognostic factors. Application of propensity-score matching involves estimation of the propensity score followed by matching of patients according to their estimated propensity score and comparison of outcomes in matched patients. To estimate the propensity score, we fitted a logistic regression model for the receipt of high-dose methylprednisolone treatment as a function of patient demographic and hospital factors, including age, sex, JCS score, CCI, receipt of cervical spinal surgery and hospital volume. The C-statistic for evaluating the goodness-of-fit was calculated. Each patient in the high-dose methylprednisolone group was matched with a patient in the control group with the closest estimated propensity on the logit scale within a specified range (≤0.6 of the pooled SD of estimated logits) to reduce differences between treatment groups by at least 90%.[21]

Descriptive statistics of the patient population included proportions to describe categorical variables and the median and IQR values to describe continuous variables. The χ^2 test was used to compare categorical data and the Wilcoxon rank sum test to compare continuous variables. Fisher's exact test was used to compare in-hospital mortality and major complication rates between the high-dose methylprednisolone group and the control group. A logistic regression analysis for major in-hospital complications was performed in the propensity score-matched patients to analyse the adjusted effects of various factors, while also adjusting for clustering of patients within hospitals using a generalised estimating equation. The threshold for significance was a p value<0.05. All statistical analyses were conducted using IBM SPSS V.19.0 (IBM SPSS, Armonk, New York, USA).

RESULTS

We identified 3508 cervical SCI patients (2652 men and 856 women; mean±SD age, 60.8±18.7 years) who had an emergency admission direct to the participating hospitals. Among them, we identified 824 (23.4%) patients who received ≥5000 mg methylprednisolone with initiation on the day of admission (high-dose methylprednisolone group). We also identified 2101 patients treated without methylprednisolone, or with <500 mg methylprednisolone during hospitalisation (the control group). By one-to-one propensity-score matching, 812 pairs of the high-dose methylprednisolone and control groups were selected. The C-statistic for goodness-of-fit was 0.630 in the propensity-score model, which suggested a moderately good fit.

Table 1 shows the patient demographics of the unmatched and propensity-matched groups. In the unmatched groups,

Table 1 Patient demographics in unmatched and propensity score-matched groups

	Unmatched group			Propensity-matched group		
	Control (n=2101)	High-dose methyl-prednisolone (n=824)	p Value	Control (n=812)	High-dose methyl-prednisolone (n=812)	p Value
Sex (males, n (%))	1570 (74.7)	645 (78.3)	0.044	650 (80.0)	634 (78.1)	0.329
Age (years, n (%))						
≤59	786 (37.4)	318 (38.6)	0.022	292 (36.0)	313 (38.5)	0.674
60–69	513 (24.4)	219 (26.6)		218 (26.8)	216 (26.6)	
70–79	456 (21.7)	198 (24.0)		213 (26.2)	195 (24.0)	
≥80	346 (16.5)	89 (10.5)		89 (11.0)	88 (10.8)	
Charlson Comorbidity Index (n (%))						
1	1414 (67.3)	456 (55.3)	<0.001	464 (57.1)	456 (56.2)	0.638
2	508 (24.2)	287 (34.8)		279 (34.4)	276 (34.0)	
≥3	179 (8.5)	81 (9.8)		69 (8.5)	80 (9.9)	
Japan Coma Scale at admission (n (%))						
0 (alert)	1811 (86.2)	689 (83.6)	0.085	692 (85.2)	681 (83.9)	0.622
1–3 (drowsy)	200 (9.5)	99 (12.0)		95 (11.7)	97 (11.9)	
10–30 (somnolence)	36 (1.7)	20 (2.4)		15 (1.8)	18 (2.2)	
100–300 (coma)	54 (2.6)	16 (1.9)		10 (1.2)	16 (2.0)	
Cervical spinal surgery	221 (10.5)	189 (22.9)	<0.001	192 (23.6)	178 (21.9)	0.408
Preoperative length of stay (days, median (IQR))	8 (1–17)	8 (1–18)	0.838	8 (2–18)	8 (1–17)	0.683
Use of tracheostomy	55 (2.6)	51 (6.2)	<0.001	38 (4.7)	48 (5.9)	0.268
Hospital volume (per year, median (IQR))	7 (4–12)	8 (4–13)	0.004	7 (4–13)	7.5 (4–13)	0.188

patients who were male, younger, or with higher CCI were more likely to receive high-dose methylprednisolone treatment. The high-dose methylprednisolone patients were admitted to hospitals of significantly higher volume than the control group. The high-dose methylprednisolone group was significantly more likely to receive cervical spinal surgery. After propensity-score matching, patient distributions were closely balanced between the high-dose methylprednisolone and the control groups.

Table 2 shows the in-hospital mortality and major complication rates in the unmatched and propensity-matched groups. Fisher's exact test in the propensity-matched groups showed no significant difference in in-hospital mortality between the high-dose methylprednisolone and control groups (2.8% vs 3.0%, p=0.884). There was a significant difference in gastrointestinal ulcer/bleeding (8.4% vs 3.8%, p=0.001) between the groups. The high-dose methylprednisolone group demonstrated a significantly higher risk of overall major complications than the control group (17.7% vs 11.8%, p=0.001). Table 3 shows the results of logistic regression analysis for the occurrence of major complications. After adjustment for the measured confounders, the high-dose methylprednisolone group was significantly more likely to have major complications than the control group (OR, 1.66; 95% CI 1.23 to 2.24; p=0.001).

DISCUSSION

In this retrospective study using a national administrative database, patients receiving high-dose methylprednisolone after cervical SCI had a significantly higher risk of complications than those without high-dose methylprednisolone treatment. A propensity score-matched analysis revealed an increased risk of gastrointestinal ulcer/bleeding and overall major complications in the high-dose methylprednisolone group. However, high-dose methylprednisolone treatment was not associated with any increase in mortality.

Strengths and weaknesses of the study

The major strength of this study is the large size of our study sample. With a study population of 3508 patients with cervical SCI, the current analysis is the largest to examine risks associated with high-dose methylprednisolone administration. Use of the

Table 2 In-hospital mortality and major complication rates in unmatched and propensity score-matched groups

	Unmatched group			Propensity-matched group		
	Control (n=2101)	High-dose methylprednisolone (n=824)	p Value	Control (n=812)	High-dose methylprednisolone (n=812)	p Value
In-hospital mortality (n (%))	71 (3.4)	23 (2.8)	0.485	24 (3.0)	23 (2.8)	0.884
Major complications (n (%))	191 (9.1)	151 (18.3)	<0.001	96 (11.8)	144 (17.7)	0.001
Respiratory complications	84 (4.0)	53 (6.4)	0.006	39 (4.8)	49 (6.0)	0.324
Urinary tract infection	52 (2.5)	29 (3.5)	0.133	32 (3.9)	29 (3.6)	0.698
Sepsis	16 (0.8)	10 (1.2)	0.273	6 (0.7)	10 (1.2)	0.330
Gastrointestinal ulcer/bleeding	66 (3.1)	71(8.6)	<0.001	31 (3.8)	68 (8.4)	<0.001
Pulmonary embolism	1 (0.05)	4 (0.5)	0.024	1 (0.1)	4 (0.5)	0.218
Length of stay (median (IQR))	16 (6–37)	27 (10–52)	<0.001	23 (8–46)	26 (10–52)	<0.001