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Differential Effects of Culture-expanded Bone Marrow Cells on the Regeneration of Bone Between the Femoral and the Tibial Lengthenings

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Background: Transplantation of culture-expanded bone marrow cells (BMC) and platelet-rich plasma (PRP) during limb lengthening shorten the treatment period by accelerating callus formation, but the direct effects of BMC and PRP on the regeneration of the bone have not been determined.

Methods: Fifty-one bones (23 femora, 28 tibiae) in 28 patients (17 males, 11 females), with an average age of 15.0 ± 3.21 years, were lengthened by treatment with BMC and PRP. Clinical outcome was compared between the 51 bones with BMC and PRP treatment and the 60 bones without cell therapy. The parameters including age at surgery, length gained, healing index (HI), number of BMC, bone-specific alkaline phosphatase (BAP) activity of BMC, and PRP concentration, were compared between the femur and the tibia treated with BMC and PRP. Linear regression analysis was then performed to correlate the HI and other variables.

Results: The HI of the BMC and PRP groups was significantly lower than that of the control group. Average HI, amount of lengthening, number of BMC, BAP activity, and PRP concentration were 30.0 ± 6.72 days/cm, 8.10 ± 2.90 cm, 1.35 ± 0.56×10^7, 9.02 ± 3.98 U/L, and $2.4 \pm 0.7 \times 10^6$ /UL, respectively. There were no significant differences in the length gained, the number and BAP activity of BMC, and the PRP concentration between the femur and the tibia. Femoral lengthening showed significantly faster healing than tibial lengthening, although the age at surgery was significantly older in femoral lengthening. A negative relationship between the HI and the length gained was observed in the tibia. In the femur, there was a negative linear relationship between the HI and the number and BAP activity of BMC, whereas no significant correlations were detected in the tibia.

Conclusions: In femoral lengthening, decrease in the HI was remarkable by BMC and PRP transplantation, and there was a progressive increase in bone healing as the number and the osteoblastic differentiation of transplanted BMC increased. Our results suggested that regionally varying bone-forming processes by cell transplantation might be related to local blood supply and soft tissue covering.

Level of Evidence: Therapeutic retrospective study, level III.

Key Words: limb lengthening, bone marrow cells, platelet-rich plasma, cell transplantation, osteoblastic differentiation

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Limb lengthening has been used for the treatment of bone loss after trauma, congenital deficiencies, or tumor resection. This technique allowed reconstructive surgeons not only to lengthen the limb but also to correct angular and rotational deformities simultaneously. The treatment period, however, is long, which results in higher rates of complications such as pin track infection, adjacent joint contractures, delayed consolidations, and fractures. Acceleration of callus formation is essential for limb lengthening to minimize the treatment period and reduce associated complications. Tissue engineering strategy, which consists of 3 essential components (application of osteogenic cells, osteoinductive factors, and a scaffold), has emerged as a possible alternative to accelerate bone regeneration at the distracted gap.

Bone marrow-derived mesenchymal stem cell (BMC) can be easily manipulated ex vivo and directed toward the osteogenic lineage if cultured in the presence of dexamethasone.[1] Platelet-rich plasma (PRP) contains several osteoinductive growth factors that enhance and accelerate bone regeneration pathways.[2] Moreover, PRP can be a suitable carrier for BMC transplantation because it coagulates immediately by an addition of thrombin and calcium. We have introduced a novel cell therapy of BMC and PRP transplantation in lower limb lengthenings.[3] Retrospective comparative studies with and without cell transplantation demonstrated that transplantation of culture-expanded BMC and PRP into the distracted callus shortened the treatment periods and reduced the associated complications by accelerating new bone regenerates.[4,5] Favorable clinical outcome was observed, especially in the femoral lengthening rather than the tibial lengthening by treatment with BMC and PRP although

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the effects of the transplanted cells on the regeneration of the bone have not been determined.

In this study, the clinical outcome of the 51 lower limb lengthenings treated with BMC and PRP was retrospectively reviewed and compared between the femur and the tibia. Various factors that may influence the outcome of this cell therapy, including the number of transplanted BMC, osteoblastic differentiation of BMC, and platelets concentration in PRP, were then statistically analyzed to determine the effect of cell transplantation on the regeneration of the bone.

METHODS

BMC and PRP Transplantation

The methods of BMC culture and PRP preparation have been described previously.[3] For the preparation of the autologous serum for in vitro culture, 200 mL of venous blood was drawn from the patient before surgery. Approximately 40 mL of bone marrow aspirates were collected from the iliac crest during surgery and harvested with sodium heparin and Dulbecco modified Eagle medium (Sigma, St Louis, MO) supplemented with penicillin-streptomycin (Invitrogen, Carlsbad, CA), 10% patients' serum, 10^{-7} mol/L dexamethasone (Sigma), 10 mmol/L β-glycerophosphate (Sigma), and 50 μg/mL ascorbic acid phosphate (Sigma). Mononuclear cell fractions were isolated and cultured in the differentiation medium for osteoblastic differentiation. When culture dishes became semiconfluent, the adherent cells were dissociated and suspended for continued passages. The third-passaged (P3) BMC cultured for nearly 3 weeks were used for transplantation. Before transplantation, the culture media were examined for contaminations of bacterium, fungus, mycoplasma, and pathological viruses such as hepatitis B, hepatitis C, and cytomegalovirus. For the evaluation of osteoblastic differentiation of BMC, the bone-specific alkaline phosphatase (BAP) activity of the culture medium in which the P3 cells were incubated for 3 days was measured using commercially available enzyme immunoassay (SRL Inc, Japan).

Colleting venous blood and preparation of PRP were commenced within 48 hours before transplantation for fear of a decline in platelet function and increased risk of serious complication from bacterial contamination. PRP was prepared from approximately 200 mL of venous blood according to the method of Marx et al.[6] After the second centrifugation, total amount of PRP was finally adjusted according to the number of injection sites (4 to 5 mL of PRP per injection) by removing the superficial plasma. Processed PRP was then stored with agitation at room temperature until transplantation. A sample of PRP was also used for the determination of platelet count after processing.

The transplantation technique of BMC and PRP has been described previously.[3] At the operating room, BMC were dissolved in a PRP, and 5000 U of human thrombin was mixed with 2 meq of calcium gluconate. Then, 2 18-G needles were inserted at the distracted callus face to face with each tip. Two milliliters of a thrombin-calcium mixture and 4 to 5 mL of a BMC and PRP solution were injected simultaneously into the callus so that the PRP gel might develop within the injected site.

Patients

After the approval of the Institutional Review Board of Nagoya University Hospital in 2002, transplantation of BMC and PRP was performed in the patients who made a choice of this treatment, and provided written, informed consent according to the format of the Institutional Review Board. Inclusion criteria of this study were the patients who were lengthening the long bones with BMC and PRP transplantation and followed up at least 3 months after removal of the fixator. Indications for limb lengthening were the patients who have a limb length discrepancy over 3 cm or who are of stature shorter than −3 standard deviation secondary to skeletal dysplasias, congenital deficiencies, or endocrine conditions. The surgical technique and the distraction schedule were standardized in all patients. The proximal diaphyseal osteotomy was subcutaneously performed by multiple drill holes followed by an osteotome. After an initial delay (7 to 14 d), gradual distraction of 1 mm per day was commenced. The distraction rate was adjusted considering the callus formation on the radiographs and the range of movement of the adjacent joints. The physiotherapy regimen was also standardized in all patients. No postoperative immobilization was used and weightbearing with crutches was encouraged from the seventh postoperative day, depending on patient tolerance. For patients with a short stature, simultaneous lengthening of bilateral femora or bilateral tibiae was performed and BMC and PRP transplantation was done bilaterally. The decision to remove the fixator was made by at least 3 pediatric orthopaedists based on the radiologic appearance of the regenerated bone (continuity of at least 3 cortices with reformed medullary cavity).

Fifty-one bones in 28 patients were included in the study (Table 1). Twenty-three procedures were carried out in the femur and 28 in the tibia. There were 17 male and 11 female patients with an average age of 15.0 ± 3.21 years. Eleven had achondroplasia, 3 hypochondroplasia, 4 hormonal abnormalities, 4 other bone dysplasias, 3 longitudinal deficiencies (congenital pseudarthrosis of the tibia in 1, hemiatrophy in 1, and scleroderma in 1, respectively), and 3 had posttraumatic growth arrest. Orthofix monolateral external fixator (Orthofix SRL, Verona, Italy) was used for 9 femora and 7 tibiae, DynaFix rail deformity system (EBI; Parsippany, NJ) for 12 femora and 19 tibiae, and EBI multiaxial correction system (EBI; Parsippany) for 2 femora and 2 tibiae. All of the corrections were done gradually. The total length gained was determined from the radiographs taken before the distraction and immediately after removal of the fixator, and adjusted for the effect of magnification. The healing index (HI), which was calculated by dividing the entire external fixation time (d) by the extent of lengthening (cm), was then measured. The clinical outcome of the

TABLE 1. Details of the 51 Lengthened Bones Treated With Culture-expanded Bone Marrow Cells and Platelet-rich Plasma

Case	Age at Surgery (y)	Diagnosis	Fixator	Bone	Length Gained (cm)	HI (d/cm)	No. BMC ($\times 10^7$)	BAP (U/L)	Platelets in PRP (/μL)	Correction
1	15	Achondroplasia	Orthofix	F	10.0	23.0	0.9	6.05	NA	–
	15	Achondroplasia	Orthofix	F	10.0	23.0	0.9	6.05	NA	–
2	14	Congenital longitudinal deficiency	Orthofix	F	3.6	26.9	1.8	6.65	NA	–
3	13	Achondroplasia	Orthofix	T	10.0	23.3	1.6	4.1	NA	–
	13	Achondroplasia	Orthofix	T	10.0	18.8	1.6	4.1	NA	–
4	20	Posttraumatic growth arrest	Orthofix	T	4.5	37.6	2.8	4.7	NA	–
5	19	Achondroplasia	Orthofix	F	9.0	18.2	1.1	7.5	NA	–
	19	Achondroplasia	Orthofix	F	9.0	20.9	1.1	7.5	NA	–
6	20	Achondroplasia	Orthofix	F	7.5	29.3	1.4	12.0	NA	–
	20	Achondroplasia	Orthofix	F	7.5	29.3	2.1	12.0	NA	–
7	20	Achondroplasia	Orthofix	F	8.2	18.7	2.1	13.5	NA	–
	20	Achondroplasia	Orthofix	F	8.8	21.6	3.2	13.5	NA	–
8	18	Hypochondroplasia	Orthofix	T	8.7	32.9	3.2	4.5	NA	–
	18	Hypochondroplasia	Orthofix	T	8.7	37.6	1.6	4.5	NA	–
9	16	Achondroplasia	Orthofix	T	8.0	28.5	1.6	9.2	NA	–
	16	Achondroplasia	Orthofix	T	8.0	37.6	1.6	9.2	NA	–
10	14	Metaphyseal dysplasia	EBI (rail)	T	6.5	37.4	2.6	10.9	NA	+
	14	Metaphyseal dysplasia	EBI (rail)	T	6.5	40.6	2.6	10.9	NA	+
11	14	Achondroplasia	EBI (rail)	F	9.6	22.7	1.1	13.6	NA	–
	14	Achondroplasia	EBI (rail)	F	9.6	22.7	1.1	13.6	NA	–
12	13	Mesomelic dysplasia	EBI (rail)	T	6.0	32.5	1.9	18	2,233,000	+
	13	Mesomelic dysplasia	EBI (rail)	T	6.0	37.2	1.9	18	2,233,000	+
13	12	Congenital longitudinal deficiency	EBI (rail)	F	3.3	35.8	0.8	3.7	2,422,000	–
	12	Congenital longitudinal deficiency	EBI (rail)	T	3.3	35.8	0.8	3.7	2,422,000	–
14	18	Hypochondroplasia	EBI (rail)	T	8.8	39.7	0.7	7.6	2,030,000	+
	18	Hypochondroplasia	EBI (rail)	T	8.8	39.7	0.7	7.6	2,030,000	+
15	13	Hormonal abnormalities	EBI (rail)	T	8.5	24.6	0.8	9.1	2,984,000	–
	13	Hormonal abnormalities	EBI (rail)	T	8.5	26.2	0.8	9.1	2,984,000	–
16	11	Achondroplasia	EBI (rail)	T	8.8	35.7	1.8	7.3	3,541,000	+
	11	Achondroplasia	EBI (rail)	T	8.8	31.7	1.8	7.3	3,541,000	+
17	19	Hypochondroplasia	EBI (rail)	F	6.5	24.6	1.3	5.7	2,812,000	–
	19	Hypochondroplasia	EBI (rail)	F	6.5	24.6	1.0	5.7	2,812,000	–
18	13	Achondroplasia	EBI (rail)	T	12.0	22.7	1.0	7.5	2,210,000	+
	13	Achondroplasia	EBI (rail)	T	12.0	24.4	1.4	7.5	2,210,000	+
19	12	Spondylometaphyseal dysplasia	EBI (MAC)	T	7.0	38.4	1.4	8.7	NA	+
	12	Spondylometaphyseal dysplasia	EBI (MAC)	T	7.0	38.4	1.4	8.7	NA	+
20	16	Achondroplasia	EBI (rail)	T	12.0	29.7	1.4	5.8	608,000	+
	16	Achondroplasia	EBI (rail)	T	12.0	27.3	1.4	5.8	608,000	+
21	14	Hormonal abnormalities	EBI (rail)	F	9.0	36.4	0.3	7.4	4,850,000	+
	14	Hormonal abnormalities	EBI (rail)	F	9.0	38	0.3	7.4	4,850,000	+
22	7	Congenital longitudinal deficiency	EBI (rail)	F	10.2	23.3	0.8	7.9	2,028,000	–
23	15	Hormonal abnormalities	EBI (rail)	T	6.0	40.5	1.2	11.5	2,316,000	–
	15	Hormonal abnormalities	EBI (rail)	T	6.0	40.5	1.2	11.5	2,316,000	–
24	10	Hormonal abnormalities	EBI (rail)	T	7.5	28.8	1.15	18.7	1,628,000	–
	10	Hormonal abnormalities	EBI (rail)	T	7.5	28.8	1.15	18.7	1,628,000	–
25	19	Achondroplasia	EBI (rail)	F	9.0	29.3	1.2	8.4	1,684,000	–
	19	Achondroplasia	EBI (rail)	F	8.7	30.3	1.2	8.4	1,684,000	–
26	19	Posttraumatic growth arrest	EBI (rail)	F	9.0	31.2	0.7	9	2,785,000	–
27	13	Spondylometaphyseal dysplasia	EBI (MAC)	F	5.5	25.1	1.4	13.4	2,740,000	+
	13	Spondylometaphyseal dysplasia	EBI (MAC)	F	6.0	25.3	1.4	13.4	2,740,000	+
28	12	Posttraumatic growth arrest	EBI (rail)	F	10.0	30.8	1.2	8.2	3,202,000	–

BAP indicates bone-specific alkaline phosphatase; BMC, bone marrow cells; F, femur; HI, healing index; NA, not available because of lack of data; PRP, platelet-rich plasma; T, tibia.

60 bones in 29 patients that were lengthened without additional cell therapy was reviewed as controls.

Statistical Analysis

The clinical values of age at surgery, amount of lengthening, the HI, number of transplanted BMC, BAP activity of BMC, and platelets concentration in PRP were shown as the average ± standard deviation. Differences in the outcome variables between the treatment groups were statistically analyzed by the Mann-Whitney *U* test for nonparametric data. As the HI between the femur and the tibia treated with BMC and PRP was different, lineal regression analysis was performed in the femur and the tibia separately to correlate the HI and other variables. Statistical significance was set at a *P* value of less than 0.05. Data analysis was performed using JMP version 6 (SAS Institute, Cary, NC).

RESULTS

Preoperatively intended lengths were obtained in all segments and the average HI was 30.0 ± 6.72 days/cm. The average length gained was 8.10 ± 2.90 cm, which resulted in the average percentage of lengthening which was 35.3 ± 13.3% of the original bone length. The average number of BMC for transplantation was $1.35 \pm 0.56 \times 10^7$. BAP activity in the culture medium was averaged at 9.02 ± 3.98 U/L. Platelets concentration in PRP for transplantation was averaged at $2.4 \pm 0.7 \times 10^6/\mu L$. Simultaneous gradual correction of deformity was performed in 18 bones (14 tibiae and 4 femora). Superficial pin track infection was commonly observed, especially in the femoral lengthening but was successfully treated with oral antibiotics. Complications that required an additional treatment occurred in 6 bones. Four patients had a fracture after the removal of the fixation device, 3 of them were femoral fractures treated by skin traction and 1 was a tibial fracture treated by above-knee plaster cast immobilization. Two patients required subcutaneous osteotomy for early consolidation during femoral lengthening. Overall complications occurred at an average of 0.12 times per segment.

The average HI of the bones treated with BMC and PRP (30.0 ± 6.72 d/cm) was shown to be significantly lower than that of the bones without cell therapy (51.4 ± 26.5 d/cm) both in the femur ($P < 0.0001$) and in the tibia ($P = 0.0059$), although there was no significant difference in the age at surgery between the 2 groups (Table 2). A larger amount of lengthening was gained in the BMC and PRP groups ($P = 0.0114$).

TABLE 3. Comparison of the Parameters Between the Femoral and the Tibial Lengthenings

	Femur (N = 23)	Tibia (N = 28)	P*
Age at surgery (y)	16.1 ± 3.57	14.1 ± 2.63	0.0162†
Length gained (cm)	8.07 ± 1.97	8.12 ± 2.22	0.4307
HI (d/cm)	26.6 ± 5.46	32.7 ± 6.46	0.0013†
No. BMC ($\times 10^7$)	1.23 ± 0.62	1.45 ± 0.56	0.0855
BAP (U/L)	8.95 ± 3.38	9.08 ± 4.47	0.8128
Platelets in PRP ($\times 10^3/uL$)	2551 ± 492	2207 ± 817	0.2062

*According to the Mann-Whitney *U* test.
†Statistically significant.
BAP indicates bone-specific alkaline phosphatase; BMC, bone marrow cells; HI, healing index; PRP, platelet-rich plasma.

The average HI of femoral lengthening (26.6 ± 5.46 d/cm) was significantly lower than that of tibial lengthening (32.7 ± 6.46 d/cm) ($P = 0.0013$), although the age at surgery was significantly older in femoral lengthening (16.1 ± 3.57) than in tibial lengthening (14.1 ± 2.63) ($P = 0.0162$) (Table 3). The average amount of lengthening was 8.07 ± 1.97 cm in the femur and 8.12 ± 2.22 cm in the tibia. The average number of transplanted BMC in the femoral and tibial lengthenings was $1.23 \pm 0.62 \times 10^7$ and $1.45 \pm 0.56 \times 10^7$, respectively. The BAP activity of BMC was averaged at 8.95 ± 3.38 in the femur and 9.08 ± 4.47 in the tibia. The platelets concentration in PRP after processing had an average of $2.55 \pm 0.49 \times 10^6$ in femoral lengthening and $2.21 \pm 0.82 \times 10^6$ in tibial lengthening. There were no significant differences in the increase in length, the number and the BAP activity of BMC, and the platelets concentration in PRP.

As femoral lengthening showed significantly faster healing than tibial lengthening by BMC and PRP transplantation, the effect of cell therapy on the regeneration of the bone was analyzed separately in the femur and the tibia. There was a negative relationship between the HI and the length gained in tibial lengthenings ($P = 0.0008$) (Table 4). Age at surgery and platelets

TABLE 2. Comparison of the Parameters Between the 51 Bones With BMC and PRP Transplantation and 60 Bones Without Transplantation

	No. Bones		Age at Surgery (y)		Lengthening (cm)		Healing Index (d/cm)	
	BMC and PRP	Control	BMC and PRP	Control	BMC and PRP	Control	BMC and PRP	Control
Femur	23	25	16.1 ± 3.57	16.2 ± 4.61	8.07 ± 1.97	6.58 ± 3.03	26.6 ± 5.46	53.4 ± 23.4
			$P = 0.7389$		$P = 0.1259$		$P < 0.0001$*	
Tibia	28	35	14.1 ± 2.63	15.9 ± 3.58	8.12 ± 2.22	6.43 ± 2.85	32.7 ± 6.46	49.9 ± 28.7
			$P = 0.0386$		$P = 0.0394$*		$P = 0.0059$*	
Total	51	60	15.0 ± 3.21	16.1 ± 4.01	8.10 ± 2.90	6.50 ± 2.90	30.0 ± 6.72	51.4 ± 26.5
			$P = 0.2350$		$P = 0.0114$*		$P < 0.0001$*	

*Statistically significant.
BMC indicates bone marrow cells; PRP, platelet-rich plasma.

TABLE 4. Linear Regression Analysis of the Healing Index in Various Parameters

	Correlation Coefficient (r)		Significance Level (P)	
Parameter	Femur	Tibia	Femur	Tibia
Age at surgery (y)	−0.204	0.335	0.3527	0.0813
Length gained (cm)	−0.208	−0.608	0.3418	0.0008*
No. BMC	−0.451	0.053	0.0309*	0.7879
BAP activity	−0.425	0.136	0.0433*	0.4896
Platelets in PRP	0.129	0.115	0.6891	0.6596

*Statistically significance.
BAP indicates bone-specific alkaline phosphatase; BMC, bone marrow cells; PRP, platelet-rich plasma.

concentration in PRP did not correlate to the HI in both bones. No significant correlations were detected for the number and BAP activity of BMC in tibial lengthening. For femoral lengthening, on the other hand, there was a linear relationship between the HI and the number of BMC ($P = 0.0309$) and BAP activity (0.0433). As the number and osteoblastic differentiation of transplanted BMC increased, there was a progressive increase in bone healing in the femur (Figs. 1, 2).

DISCUSSION

Transplantation of culture expanded BMC and PRP during limb lengthening is easy to perform because BMC can be expanded and manipulated into osteoblastic lineage by culturing them in a differentiation medium, and PRP can be easily prepared from venous blood by centrifugation. Moreover, it is safe with a minimal side

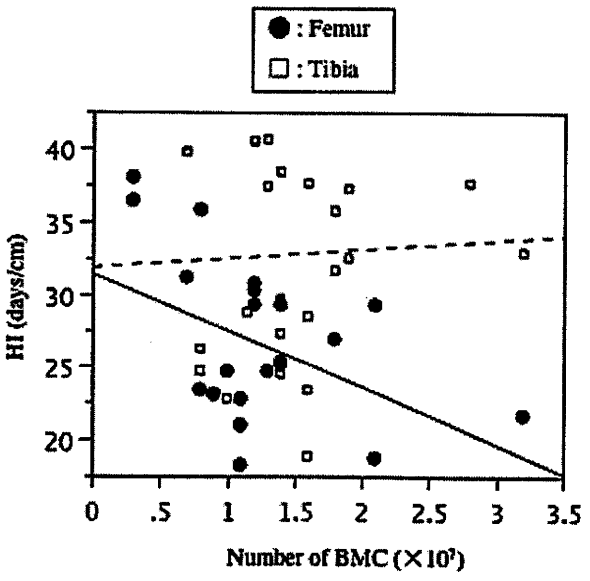

FIGURE 1. Linear regression analysis demonstrating the relationship between the healing index (HI) and the number of transplanted bone marrow cells (BMC). Significant negative correlation between the HI and the number of BMC was evident in the femur (solid line, $P=0.0309$), whereas there was no correlation between them in the tibia (dashed line, $P=0.7879$).

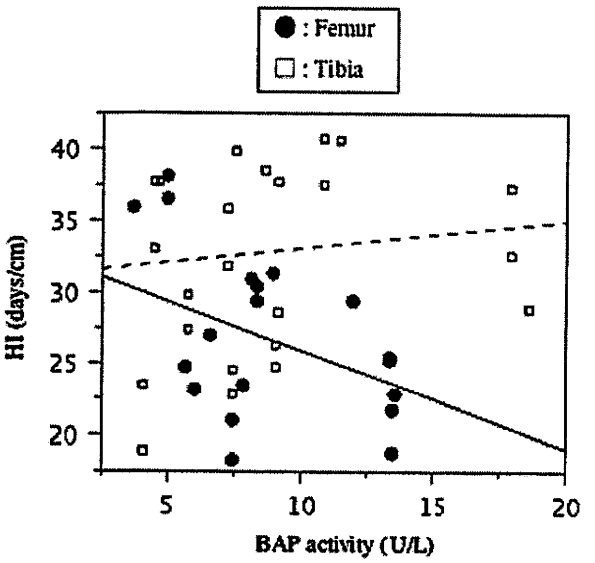

FIGURE 2. Linear regression analysis demonstrating the relationship between the healing index (HI) and the bone-specific alkaline phosphatase (BAP) activity of the transplanted bone marrow cells. Significant negative correlation between the HI and the BAP activity was evident in the femur (solid line, $P=0.0433$), whereas there was no correlation between them in the tibia (dashed line, $P=0.4894$).

effect because both BMC and PRP are autologous, which are nontoxic and nonimmunoreactive. In this study, the outcome of lengthening with BMC and PRP transplantation was reviewed and statistically analyzed based on not only clinical variables but also characteristics of transplanted cells to evaluate the efficacy of this cell therapy. We have shown that this cell therapy provided favorable effects on new bone regenerates during limb lengthening; however, it is very expensive. For 1 patient, it costs more than US$2000 including personnel expenses, culture instruments and chemicals, contamination tests, and so on. A cost-benefit analysis of this treatment will be needed.

Bone healing during limb lengthening depends on various parameters such as age at surgery and the amount of lengthening.[7–10] Generally, bone formation occurs more rapidly in younger patients. Several investigators reported a negative relationship between distraction length and healing time, which was evaluated by various parameters including HI, external fixation index, and distraction-consolidation index.[7,9,10] In this study, femoral lengthening showed faster healing than tibial lengthening irrespective of older age group and similar amount of length gained. However, there were no significant differences in the number of BMC, BAP activity, and PRP concentration between the femur and the tibia. These results suggested that the effect of BMC and PRP on the new bone regenerates might be related to the microenvironment at the transplanted sites.

The effect of an osteotomy site on new bone regenerates is controversial. Fischgrund et al[9] and

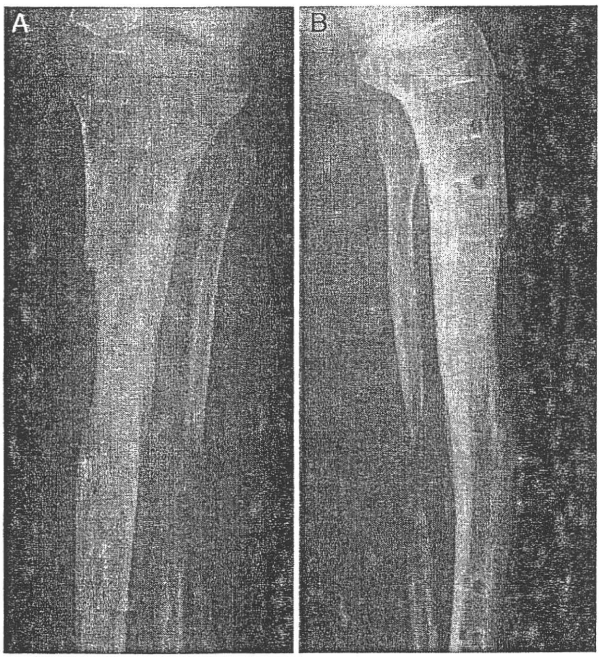

FIGURE 3. Anteroposteior (A) and lateral (B) radiographs of the left tibia of an 18-year-old man with hypochondroplasia (case 14) just after removal of the pins. Callus formation was predominant posterolaterally and extremely poor at the anteromedial aspect of the tibia.

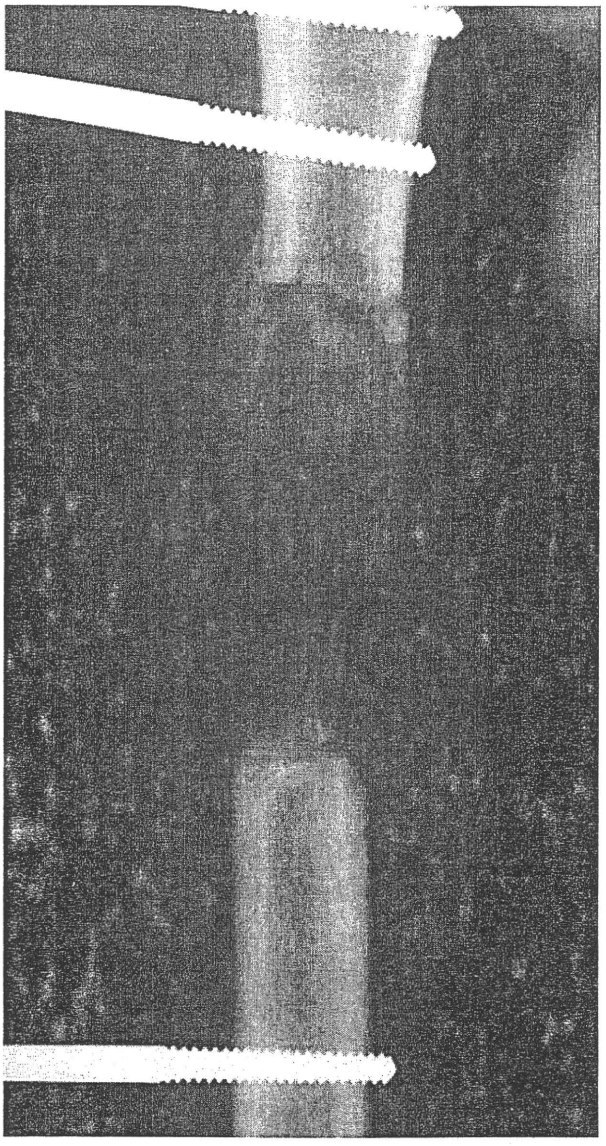

FIGURE 4. Anteroposterior radiograph of the right femur of a 19-year-old man with achondroplasia (case 5) just at the end of distraction demonstrating abundant fusiform-shaped callus formation.

Bonnard et al[11] reviewed limb lengthening procedures using the Ilizarov external fixator and noted faster bone healing in the femur than in the tibia. De Bastiani et al,[12] in contrast, reported that the HI was better for the tibia than for the femur in patients with achondroplasia whose bones were lengthened using the monolateral external fixator. Noonan et al[7] reviewed 261 limb lengthenings and documented that the healing time was relatively quicker in the femur than in the tibia but there were no significant differences in the adjusted HI between them. No significant differences in bone healing between the femur and the tibia were also reported in the studies by Donnan et al[13] and Fink et al.[14] Predominantly quicker healing in the femur may be due to the positive effect on osteogenesis of transplanted cells. For further clinical application of BMC and PRP therapy, it is necessary to determine the optimization of BMC and PRP conditions for transplantation.

Dallari et al[15] reported that a combination of BMC and PRP permits an acceleration in bone healing and bone remodeling processes in a rabbit model of bone defect. Lucarelli et al[16] stated that the proliferation of BMC promoted by 10% PRP but suppressed by high PRP concentration. The authors recently showed that a high platelet concentration in PRP in combination with BMC could accelerate the formation of new bone in the rat mode of limb lengthening.[17] In this study, the volume of extracted venous blood was standardized and the total amount of PRP was finally concentrated by removing the superficial plasma, which consequently resulted in a maximal platelets concentration in PRP. Lack of correlations between the HI and PRP concentration may be due to relatively constant platelets concentration in all but 1 patient (case 20) who could not obtain maximally concentrated PRP as a result of technical failure.

In vitro expansion of BMC offers the potential to generate a large number of osteoprogenitor cells; however, osteoblastic differentiation of BMC decreases after an expansion by several passages.[18,19] Several experimental studies showed that in vitro osteoblastic differentiation of BMC correlated with in vivo osteogenesis when these cells were transplanted with appropriate scaffolds.[18,20,21] The volume of extracted marrow samples was standardized in our protocol whereas the number of cells for transplantation, which depended on the number

of available BMC after ex vivo expansion, ranged from 3.0×10^6 to 3.2×10^7. Osteoblastic differentiation of culture expanded BMC, which also depended on individual samples and ranged from 3.7 to 18.7 U/L. In the tibia, the number and the osteoblastic differentiation of BMC did not correlate with healing, and callus formation was predominant posterolaterally and poor at the anteromedial aspect of the tibia (Figs. 3A, B). In femoral lengthening, in contrast, there was a progressive increase in bone healing as the number and the osteoblastic differentiation of BMC increased, and abundant external callus was commonly observed after cell transplantation (Fig. 4). These results suggested the crucial significance in the adequate local blood supply for bone regeneration in BMC and PRP treatment. Lucarelli et al[22] noted that the transplantation of BMC and PRP improved bone repair by accelerating vascular invasion. BMC and PRP may not only promote osteogenesis at the transplanted site but may also contribute to vascular invasion and stimulate osteoprogenitor cells that are thought to reside in the surrounding soft tissues. Regionally varying bone-forming processes by cell transplantation might be related to local blood supply and soft tissue covering. Favorable effects on bone regeneration by BMC and PRP therapy could be expected when the cells are transplanted into the area with sufficient blood supply and abundant soft tissues.

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Radiographic Analysis of Movements of the Acetabulum and the Femoral Head After Salter Innominate Osteotomy

Hiroshi Kitoh, MD, Hiroshi Kaneko, MD, and Naoki Ishiguro, MD

Background: Salter innominate osteotomy (SIO) is widely used to improve the coverage of the femoral head in dysplastic acetabulum, but the geometric change after osteotomy and its effect on the outcome have not been well elucidated.

Methods: Pelvic radiographs of the 90 hips in 86 patients who underwent SIO for the treatment of acetabular dysplasia were reviewed and the movement of the distal fragment and the shift of the femoral head after SIO were analyzed. On the basis of the anteroposterior radiographs of the pelvis in a supine position taken at 5 weeks after operation, various parameters including an open-wedged angle at the osteotomy site (lateral rotation angle, LRA), lateral displacement of the distal fragment (distance *d*), and the ratio of the bilateral obturator foramen heights (the ratio of obturator heights, ROH), were measured. Improvement in the center-edge angle (CEA) and acetabular index (AI) after SIO was correlated with the LRA, distance *d*, and ROH. Horizontal and vertical distances from the pubic symphysis to the center of the femoral head were also measured from preoperative and postoperative pelvic radiographs and changes in the position of the femoral head were calculated. For the patients who were followed until skeletal maturity, final radiographic results were also assessed according to the Severin classification.

Results: The average improvement of the CEA and AI after SIO was 19.6 and 13.3 degrees, respectively. The average value of the LRA, distance *d*, and ROH were 30.2 degrees, 4.07 mm, and 73.0%, respectively. The LRA and distance *d* positively and the ROH negatively correlated with the improvement of the CEA and AI. The center of the femoral head moved an average of 7.06 mm caudally and 3.11 mm medially after SIO. Thirty-six hips (40%) in 36 patients were available for follow-up until skeletal maturity. The radiographic outcome was good (Severin I or II) in 33 hips and poor (Severin III) in 3 hips. Preoperative CEA was relatively smaller in a poor group. Greater improvement of the CEA during postoperative follow-up was observed in a good group.

Conclusions: Favorable coverage of the femoral head was obtained after SIO by shifting the center of the femoral head caudally and medially as well as rotating the distal fragment anterolaterally. SIO is a very effective procedure in improvement of the dysplastic acetabulum for the hips with round and spherical femoral head.

Level of Evidence: Therapeutic studies, level III (retrospective study).

Key Words: Salter innominate osteotomy, radiographic analysis, acetabular dysplasia

(*J Pediatr Orthop* 2009;29:879–884)

Salter innominate osteotomy (SIO) has been the most commonly used procedure for treating acetabular dysplasia and residual subluxation in developmental dysplasia of the hip. Excellent or good results have been reported after SIO, but geometric changes of the acetabulum after SIO are not fully delineated.[1–3] The acetabulum is redirected by rotating the distal fragment anterolaterally to establish a larger weight-bearing area.[4,5] This acetabular movement takes place around an axis from the symphysis pubis to the site of the osteotomy, which results in an apparent deformity of the obturator foramen. Lateral rotation of the distal fragment could be measured by an angle of wedged bone graft placed into the resultant defect, and anterior torsion could be identified as a decrease in the height of the obturator foramen on anteroposterior (AP) radiographs of the pelvis.[6]

SIO not only increases the weight-bearing area of the acetabulum but also changes the moment of forces acting on the hip joint by shifting the center of the femoral head. Although medial shift of the femoral head would be beneficial for the hip by decreasing the moment of the forces, a lateral shift would be detrimental. The effect of SIO on the position of the femoral head, however, is still conflicting.[7–11] Changes in the position of the femoral head by SIO requires elucidation to understand the biomechanical effects of this procedure.

The effectiveness of SIO is radiographically judged by an increase in the center-edge angle (CEA) and decrease in acetabular index (AI) after operation. There is consensus on the importance of a lateral coverage of the femoral head, but differences in the amount of improvement of these parameters after SIO have been reported.[3,12–14] The reason for this difference is not clear, but it is possible that the degree of the distal fragment movement and the osteotomy technique influences the improvement of the parameters.

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In this retrospective study, the movement of the distal fragment and the shift of the center of the femoral head by SIO were radiographically assessed for the patients who were treated with this procedure in our institution. Relationships were statistically analyzed between the degree of movement of the distal fragment and the improvement of radiographic parameters including the CEA and AI, which may lead to a better understanding of the geometry of this surgical procedure. In addition, middle-term results of the SIO for the correction of dysplastic acetabulum were analyzed in the cases that were followed until skeletal maturity.

METHODS

Between 1991 and 2008, SIO were performed in 120 consecutive patients for the treatment of dysplastic acetabulum. Two patients with significant neuromuscular diseases, 15 patients who were lost to follow-up, and 10 patients who underwent simultaneous derotational varus femoral osteotomy or open reduction in association with SIO were excluded in this study. Seven patients were also excluded because their femoral heads were so deformed (Kalamchi-MacEwen classification[15] grade III or more) that the center of the femoral head could not be identified based on the pelvic radiographs. Thus, 90 hips in 86 patients, 4 patients (8 hips) receiving bilateral and 82 patients (the left side was treated in 53 hips and the right side in 29 hips) receiving unilateral treatment, were included in this study. Nine hips in 8 boys and 81 hips in 78 girls were treated. The average age of the patients at the time of surgery was 5.79 ± 0.59 years. The average duration of follow-up after surgery was 5.11 ± 2.57 years. Ten hips of the 8 patients had not been treated before this surgery. The other 80 hips had undergone treatment for developmental dysplasia of the hip earlier and showed residual acetabular dysplasia at the time of the index surgery. Nineteen hips were reduced successfully by the Pavlik harness, and 57 hips were treated by overhead traction. Conservative treatment was unsuccessful in 4 hips and they were treated by open reduction before SIO.

Our criteria for SIO, usually at the age of 5 or 6 years, are AI of 30 degrees or more or CEA of 5 degrees or less.[16] The innominate osteotomy was performed following the guidelines set by Salter,[4] except that tenotomy of the iliopsoas and adductor longus muscle was not performed. The maneuver described by Wedge and Salter[17] was used to open the osteotomy, and the cortical iliac bone graft was obtained from the iliac crest and fixed with 3 threaded Kirschner wires. SIO was always performed as an isolated procedure in this study. The child was managed with a single-leg hip spica cast for 5 weeks with the hip in approximately 30 degrees of flexion and abduction.

AP radiographs of the pelvis were routinely taken in a supine position with the hips in neutral before operation and at 5 weeks postoperatively when the cast was removed. Regular review has continued with special

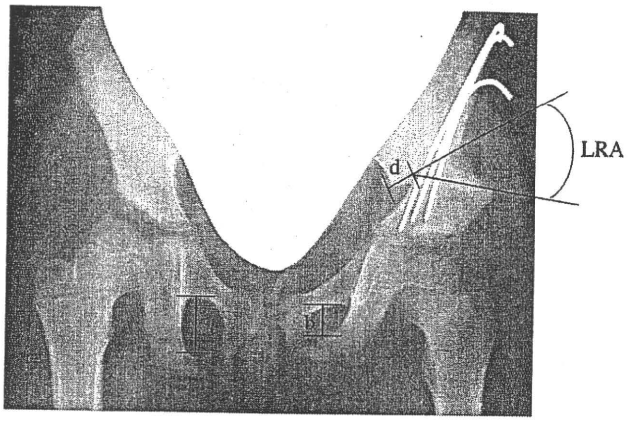

FIGURE 1. Lateral rotation angle (LRA) was defined as an open-wedged angle at the osteotomy site. Distance (*d*) was defined as lateral displacement of the distal fragment (mm). The maximum obturator foramen heights of the operated side (*b*) and the unoperated side (*c*) were measured and the ratio of the obturator height (ROH) was calculated (%).

reference to the callus formation of the osteotomy site and remodeling of the distal fragment. The AI and CEA were determined preoperatively and 5 weeks postoperatively. The most lateral point of the subchondral bone condensation in the acetabular roof (sourcil) was used as the landmark for the CEA and AI measurements. On the basis of the AP radiographs of the pelvis taken at 5 weeks after operation (just after cast removal), the following parameters were measured to evaluate the amount of movement of the distal fragment after SIO (Fig. 1). Lateral rotation angle (LRA) was defined as an open-wedged angle between the 2 fragments. Distance *d* (mm) was defines as lateral displacement of the distal fragment (positive values indicate lateral displacement and negative values indicate medial displacement). Changes in the heights of the obturator foramen after SIO (ratio of the obturator height, ROH) were calculated by the ratio of the maximum heights of bilateral foramens. Movement in the center of the femoral head was calculated from preoperative and 5 weeks postoperative radiographs of the pelvis. A Mose template was used to locate the centers of the femoral heads and their diameters were recorded. All measurements were corrected for changing magnification using the ratio of the diameters of the femoral heads on different films. The vertical and horizontal distances of the center of the femoral head from the center of the pubic symphysis were measured based on the preoperative and postoperative radiographs, and the shift of the femoral head after SIO was calculated (positive values indicate caudal or medial displacement and negative values indicate cranial or lateral displacement). For patients with skeletal maturity, radiographic results were evaluated according to the criteria proposed by Severin,[18] and were classified into 2 groups: a good group (Severin classes I and II) and a poor group (Severin classes III or more).

The measured values of the CEA, AI, LRA, distance *d*, ROH, and a shift of the center of the femoral head were shown as the average ± SD. The degree of the radiographic improvement of the CEA and AI after SIO was calculated from the preoperative and postoperative AP radiographs of the pelvis, and correlated with the variables representing distal fragment movements after operation (LRA, distance *d*, and ROH) using lineal regression analysis. The Mann-Whitney *U* test was used to determine the correlation between the average CEA and AI measurements and Severin's radiographic results at skeletal maturity. Statistical significance was set at a *P* value of less than 0.05. Data analysis was performed using JMP version 6 (SAS Institute, Cary, NC).

RESULTS

No major complications, such as postoperative avascular necrosis, nerve palsy, flexion contracture of the hip, or deep infection, occurred in our series. None had undergone additional procedures after the index surgery. The lateral displacement of the distal fragment was intraoperatively confirmed in all hips using image intensifier, but secondary loss of correction (medial displacement) was observed in 10 hips (11.1%) at the time of cast removal. Preoperative average CEA and AI were −0.86 ± 5.53 degrees and 34.0 ± 4.39 degrees, respectively. Postoperative CEA averaged 18.7 ± 5.97 degrees and was operatively increased by 19.6 ± 5.70 degrees (range, 5 to 35 degrees). Postoperative AI averaged 20.7 ± 5.02 degrees and was reduced on an average by 13.3 ± 4.03 degrees (range, 4 to 25 degrees) (Table 1).

The average values of the LRA, distance *d*, and ROH were 30.2 ± 6.56 degrees (range, 16 to 47 degrees), 4.07 ± 3.26 mm (range, −6 to 12 mm), and 73.0 ± 15.7% (range, 32% to 114%), respectively. Lineal regression analysis showed that an increase in the CEA after SIO positively correlated with the LRA ($r = 0.32$, $P = 0.0020$) and distance *d* ($r = 0.23$, $P = 0.0277$), and negatively correlated with the ROH ($r = -0.42$, $P < 0.0001$). Similarly, a decrease in the AI after operation was strongly related with the LRA ($r = 0.54$, $P < 0.0001$), distance *d* ($r = 0.41$, $P < 0.0001$), and ROH ($r = -0.47$, $P < 0.0001$) (Table 2). The interrelationship among the LRA, distance *d*, and ROH is summarized in Table 3. There was a strong correlation between the distance *d* and the LRA ($r = 0.62$, $P < 0.0001$). The ROH correlated negatively with the distance *d* ($r = -0.35$, $P = 0.0008$) and the LRA ($r = -0.48$, $P < 0.0001$).

TABLE 1. Improvement of the CEA and AI After SIO

	Preoperative	Postoperative	Change
CEA (degrees)*	−0.86 ± 5.53	18.7 ± 5.97	19.6 ± 5.70
AI (degrees)*	34.0 ± 4.39	20.7 ± 5.02	13.3 ± 4.03

AI indicates acetabular index; CEA, center-edge angle; SIO, Salter innominate osteotomy.
*Average ± SD.

TABLE 2. Relationship Between Improvement of the Radiographic Parameters and Variables of the Distal Fragment Movement (LRA, Distance *d*, and ROH)

Variables	Correlation With Improvement of the CEA	Correlation With Improvement of the AI
LRA	$r = 0.32$ ($P = 0.0020$*)	$r = 0.54$ ($P < 0.0001$*)
Distance d	$r = 0.23$ ($P = 0.0277$*)	$r = 0.41$ ($P < 0.0001$*)
ROH	$r = -0.42$ ($P < 0.0001$*)	$r = -0.47$ ($P < 0.0001$*)

AI indicates acetabular index; CEA, center-edge angle; LRA, lateral rotation angle; ROH, ratio of the obturator height.
*Statistically significance.

The center of the femoral head moved caudally in all hips, and the average downward shift of the head was 7.06 ± 3.23 mm (range, 1 to 15 mm) after SIO. It moved medially to an average of 3.11 ± 3.22 mm (range, −5 to 14 mm). The center of the femoral head horizontally remained unchanged in 9 hips, moved laterally in 9 hips, and moved medially in 72 hips (Fig. 2). There was a positive correlation between a caudal shift and a medial displacement of the femoral head after SIO ($r = 0.25$, $P = 0.0165$).

Thirty-six hips (40%) in 36 patients were available for follow-up after the patients had reached skeletal maturity. The preoperative and postoperative CEA averaged −0.36 ± 4.51 degrees and 18.4 ± 4.93 degrees, respectively. The CEA at the final examination averaged 26.4 ± 6.27 degrees and improved to 8.06 ± 6.52 degrees during postoperative follow-up (Fig. 3). The radiographic outcome was good (Severin I or II) in 33 hips (31 female and 2 male, the left side in 23 and right in 10) and poor (Severin III) in 3 hips (all were female, the left side in 2 and right in 1). The average age at operation was 5.89 ± 0.61 years in a good group and 6.33 ± 0.80 in a poor group, which was not statistically significant. Table 4 summarized the relationship between the final outcome and the radiographic parameters. The average preoperative CEA was −0.03 ± 4.38 degrees in a good group and −4.00 ± 5.20 degrees in a poor group. The postoperative CEA was averaged 18.7 ± 4.96 degrees in a good group and 14.7 ± 3.06 in a poor group. There were no significant differences in the preoperative and postoperative CEA between the 2 groups, although a good group tended to have better CEA. The average improvement of the CEA during postoperative follow-up was larger in a good group (8.76 ± 1.07 degrees) compared

TABLE 3. Interrelationship Among the Variables of the Distal Fragment Movement (LRA, Distance *d*, and ROH)

	Correlation Coefficient (*r*)	Significance Level (*P*)
Distance d vs. LRA	0.62	< 0.0001*
Distance d vs. ROH	−0.35	0.0008*
LRA vs. ROH	−0.48	< 0.0001*

LRA indicates lateral rotation angle; ROH, ratio of the obturator height.
*Statistically significance.

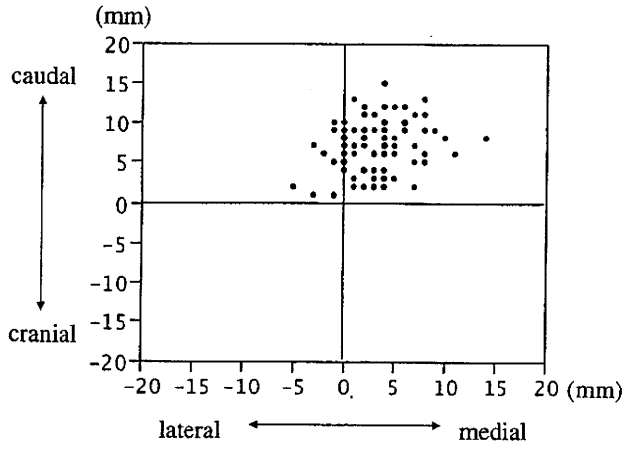

FIGURE 2. Scatterdiagram showing postoperative movement of the center of the femoral head. The femoral head moved an average of 7.06 ± 3.23 mm caudally and 3.11 ± 3.22 mm medially after Salter innominate osteotomy.

TABLE 4. Relationship Between the Radiographic Results and Average Measurements

Variables	Good Group (n = 33)	Poor Group (n = 3)	Significance*
CEA (degrees)†			
Preoperative	−0.03 ± 4.38	−4.00 ± 5.20	$P = 0.1963$
Postoperative	18.7 ± 4.96	14.7 ± 3.06	$P = 0.1145$
Final examination	27.5 ± 5.29	15.0 ± 5.29	$P = 0.0049$‡
Improvement during follow-up	8.76 ± 1.07	0.33 ± 6.11	$P = 0.0543$
AI (degrees)†			
Preoperative	33.2 ± 3.46	34.3 ± 2.89	$P = 0.4166$
Postoperative	20.4 ± 4.74	25.0 ± 3.00	$P = 0.0898$
Sharp angle (degrees)†			
Final examination	42.3 ± 3.14	47.3 ± 3.79	$P = 0.0330$‡

AI indicates acetabular index; CEA, center-edge angle.
*As determined by Mann-Whitney *U* test.
†Average ± SD.
‡Statistically significance.

with a poor group (0.33 ± 6.11 degrees), although differences were not statistically significant ($P = 0.0543$).

DISCUSSION

A favorable outcome after SIO in repairing the dysplatic acetabulum has been reported by many investigators,[1–5,12–14] but the factors influencing the effectiveness of this procedure have not been fully delineated. This study examined movements of the distal fragment and the femoral head by SIO that would affect the final outcome of this procedure. In our series, the average correction of the CEA (19.6 degrees) and the AI (13.3 degrees) obtained by SIO was within the range of correction reported in most studies.[2,7,13,19] The radiographic improvement was accompanied by movements of the distal fragment in approximately 30 degrees of lateral rotation, 4 mm of lateral displacement, and 30% decrease in the height of obturator foramen (Figs. 4A, B). The more the distal fragment moved, the better the femoral head was covered. With regard to the surgical technique, we pulled the distal fragment anterolaterally using the Charnley bone clamp after completion of the osteotomy by the Gigli saw, and then applied the maneuver technique so that the maximal anterolateral rotation of the fragment was achieved. As the distance *d* was correlated with the LRA and ROH, pulling out the distal fragment anterolaterally before the maneuver would be crucial in our surgical technique to obtain the maximal movement of the acetabulum.

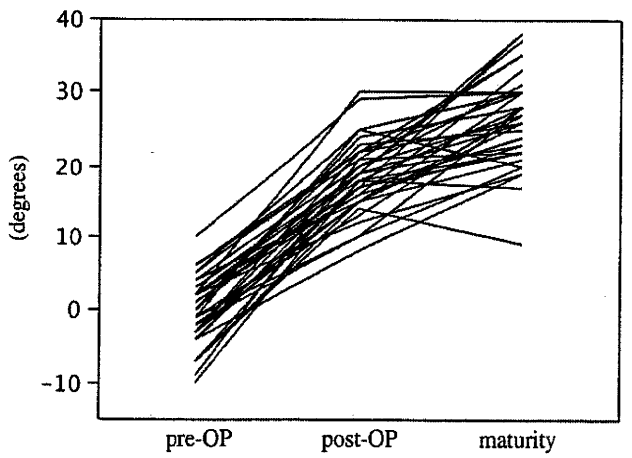

FIGURE 3. Sequential changes of the center-edge angle in 36 patients who were followed up until skeletal maturity.

The surgical technique described here is not the same that was described by Salter[4] with regard to omitting the adductor and the iliopsoas tenotomy. It may affect opening the osteotomy site and movement of the acetabulum, but we did not have difficulty in obtaining satisfactory correction in this study. Vengust et al[2] suggested that the acetabulum was not corrected to the maximum degree to eliminate the increase of the hip joint pressure when leaving the iliopsoas muscle intact. In our series, however, none has developed avascular necrosis or chondrolysis after SIO although the distal fragment was maximally opened by the maneuver technique without tenotomy of the iliopsoas muscle. Our study showed that tenotomy of the adductor and the iliopsoas muscle may be unnecessary in SIO for correcting the dysplastic acetabulum.

There are some limitations in this study because of the 2-dimensional measurements on a 3-dimensional object. Radiographic measurements of the hip joint will be affected by lumbar lordosis and the pelvic tilt in the sagittal plane. The hip spica casting frequently results in a decrease in the lumbar lordosis; thus, the accuracy of the radiographic assessments at 5 weeks postoperatively would be a concern. The LRA as measured from the AP radiographs does not accurately depict the true angle of the wedge, as the x-ray projection is oblique to the fragment. In this measurement technique, the LRA will be larger than the actual wedge.

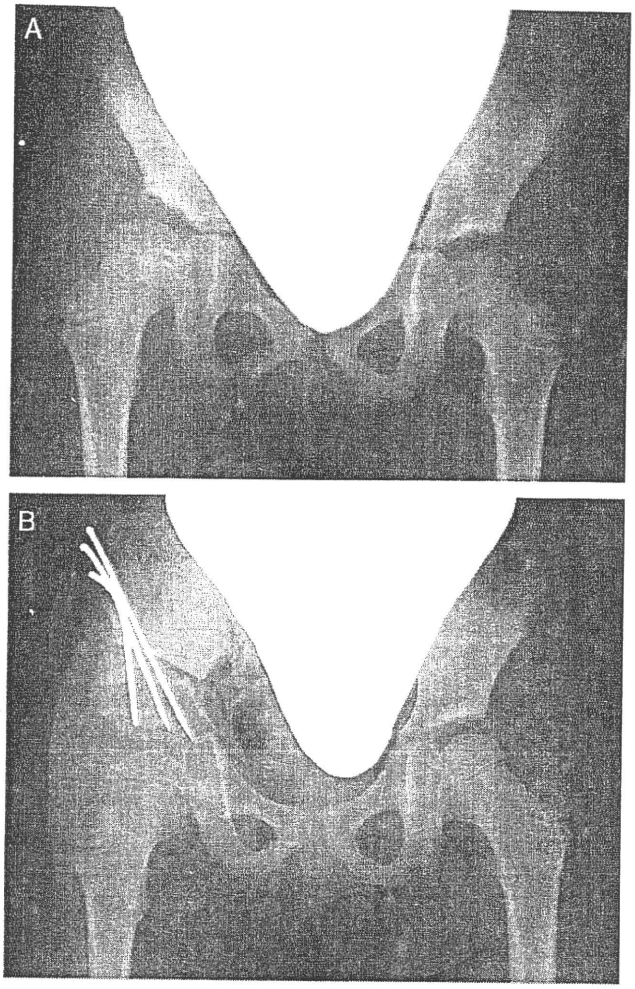

FIGURE 4. Anteroposterior radiographs of the pelvis of a 5-year-old girl with residual acetabular dysplasia of the right hip. Developmental dislocation of the right hip was conservatively reduced by overhead traction at the age of 10 months. Preoperative radiograph (A) indicated center-edge angle (CEA) of 1 degree, acetabular index (AI) of 33 degrees. Radiograph 5 weeks after surgery (B) showed CEA of 20 degrees and AI of 12 degrees. The distal fragment was rotated anterolaterally by the lateral rotation angle of 31 degrees, distance *d* of 6 mm, and the ratio of the obturator height of 67%. The center of the femoral head was moved 9 mm caudally and 3 mm medially after surgery.

Not only did the acetabulum moved to a more favorable position, but the center of the femoral head shifted an average of 7 mm caudally and 3 mm medially in this study. Earlier studies have shown that the femoral head moved caudally after SIO, but the horizontal movement of the head is still controversial.[7–11] Although the medial shift would be beneficial to the hip by decreasing the moment of the forces acting on the joint, the lateral shift would be detrimental. Utterback and MacEwen[7] discussed an increase in the distance from the body midline to the femoral head, but Radin and Paul[8] believed that SIO did not significantly alter the magnitude or direction of the resultant forces on the hip. Wong-Chung et al[9] reported the distance from the center of the femoral head to the body midline remained unchanged in 12, moved medially in 2, and moved laterally in 1 hip. They concluded that a correctly performed SIO does not significantly alter the distance from the center of the femoral head to the midline of the body. Rab[10] showed that the center of the hip joint moved 12 mm medially. Pfeifer et al[11] biomechanically showed that the hip joint was translated medially and caudally after SIO, and the length of gluteus medius and maximus muscle increased. They stated that the SIO leads to a reduction of hip joint and muscle forced in addition to increasing joint contact area. In this study, the center of the femoral head moved caudally in all cases and medially in the majority of cases after SIO, and correlations were observed between the downward shift and medial movements of the femoral head. Therefore, a correctly performed SIO increases the CEA and decreases the moment forces acting on the hip joint by displacing the distal fragment anterolaterally and shifting femoral head medially.

A similar percentage of the good radiographic results obtained after SIO has been reported by Gulman et al[13] (71% in 52 hips), Morin et al[14] (74% in 180 hips), Ito et al[3] (74% in 35 hips), and Vengust et al[2] (73% in 44 hips), although the classification as a normal hip at skeletal maturity varies among the studies. According to the radiographic criteria set by Severin,[18] we showed that 33 hips (91.7% in 36 hips) showed a good result at skeletal maturity. In this study, however, patients with aseptic necrosis of the femoral head established before the operation were excluded because accurate location of the center of the femoral head was difficult using a Mose template. Morin et al[14] and Ito et al[3] showed that preexisting necrosis of the femoral head made the prognosis for hips treated with SIO much less predictable. Excluding the hips with significant femoral head deformity may be a reason why this study showed better radiographic results than earlier reports.

The 3 hips that showed a poor result at skeletal maturity had a relatively smaller preoperative CEA and limited improvement of the acetabular development during postoperative follow-up. Vengust et al[20] reported that the average increase of the CEA during follow-up after SIO is smaller in the operated hips than in the contralateral nonoperated hips. They suggested that an unfavorable stress distribution is connected to the decrease of the CEA over time. The steep rise in the hip joint pressure after osteotomy could result in temporary impairment of acetabular development. As there were no significant differences in the degree of CEA improvement after operation between a good (19.0 degrees) and a poor group (18.7 degrees) in this study, we could not determine the reasons why some hips showed less improvement during postoperative follow-up. Overall, satisfactory Severin grade at skeletal maturity was achieved by SIO for the dysplastic acetabulum without femoral head deformities, although it does not always guarantee a good outcome in middle age. In conclusion, SIO is a very

effective procedure for the dysplastic hips with round and spherical femoral head by rotating the distal fragment anterolaterally and shifting the femoral head caudally and medially.

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Predictive Factors for Unsuccessful Treatment of Developmental Dysplasia of the Hip by the Pavlik Harness

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Background: The Pavlik harness is a widely used and effective means of initial treatment of developmental dysplasia of the hip (DDH), but some hips fail to stabilize with the use of harness and avascular necrosis (AVN) of the femoral head can occur. Predictive factors for unsuccessful Pavlik harness treatment should be determined for appropriate indication of the treatment and prevention of AVN.

Methods: The outcome of Pavlik harness treatment for DDH was retrospectively examined in 221 hips of 210 patients who were treated initially at our institution and followed up for at least 1 year after the application of the harness. Univariate analysis was performed to determine predictors for failure of reduction and for the incidence of AVN by using the Mann-Whitney *U* test for continuous variables and the Fisher exact test or the Pearson test for categorical variables. Next, independent multivariate predictors for the failure of reduction and the incidence of AVN were identified using logistic regression analysis.

Results: One hundred and eighty-one hips were reduced and the overall rate of reduction was 81.9%. AVN that was diagnosed according to the criteria of Salter et al was identified in 16 of the 181 reduced hips and the rate of incidence of AVN was 8.8%. Bilaterality and decreased distance "*a*," as defined by Yamamuro and Chene, were statistically significant univariate and multivariate risk factors for the failure of reduction. Between them, distance *a* was the most powerful predictor. Adduction contracture of the hip (abduction with the hips flexed to 90 degrees < 60 degrees) was the only significant univariate and multivariate predictor for the incidence of AVN.

Conclusions: Distance *a* and adduction contracture of the hip were important predictors for the outcome of Pavlik harness treatment. We concluded that the Pavlik harness is a very safe and effective means of DDH treatment for the hips with abduction ≥ 60 degrees and distance $a \geq 6$ mm.

Level of Evidence: Therapeutic studies, level III (retrospective study).

Key Words: developmental dysplasia of the hip, Pavlik harness, failure of reduction, avascular necrosis, predictive factors

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The Pavlik harness is a widely used and effective means of initial treatment of the developmental dysplasia of the hip (DDH) in patients under the age of 6 months.[1,2] It is considered to have a favorable rate of hip reduction and a low incidence of complications such as avascular necrosis (AVN) of the femoral head. On the basis of previous studies examining more than 100 DDH treated with the Pavlik harness, the reported rate of reduction ranges from 79% to 96% and the incidence of AVN from 0% to 22%.[3–13] Treatment with the harness, however, does not always provide a good result, as some hips fail to stabilize with the use of harness and AVN can occur. AVN is a serious iatrogenic complication and treatment is often unsatisfactory.[14] The vascular disturbance to the secondary epiphysis and the growth plate of the proximal femur leads to joint deformity, limb length discrepancy, and subsequent arthrosis. Greater effort should be made to prevent AVN in Pavlik harness treatment.

Predictive factors for unsuccessful Pavlik harness treatment (the hips that were unreduced or reduced followed by AVN) should be determined for appropriate indication of the treatment and prevention of AVN. Although several investigators have reported various predictors of treatment failure including male gender,[15] initial irreducibility,[16] bilateral dislocation,[10,16] severe dislocation,[5,9,10,17] and age at the time of Pavlik harness initiation,[7,9,16,18] it is still uncertain in the selection of patients for the harness and indications for abandoning the treatment. In conducting a retrospective study using univariable and multivariable analyses, we investigated the predictors that may contribute to incomplete reduction and the incidence of AVN for the patients with DDH treated at our institution. The purpose of this study was to determine the factors predictive for the outcome of the Pavlik harness treatment and to establish criteria for safe and effective application of this treatment.

METHODS

The Pavlik harness has routinely been used in our institution to treat infant hip subluxation and dislocation, but it has not been applied for hips with acetabular dysplasia without displacement of the proximal end of the femur. A dislocation was suspected clinically by limited abduction or shortening of the affected extremity, and a

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positive Ortolani test, which is used to determine whether the femoral head is reducible by gentle traction, abduction, and anterior translation of the thigh. Diagnosis was confirmed by an anteroposterior hip radiograph, which was routinely taken in these suspected patients, showing lateral and cephalad displacement of the proximal end of the femur accompanied by interruption of the Shenton line, or the presence of a false acetabulum. In addition, ultrasonographic screening has been adopted since 1991.

The medical records and radiographs for all patients who were treated initially with the Pavlik harness at our institution between 1987 and 2006 were reviewed and followed up for at least 1 year after the initial application of the harness. Patients who had had previous treatment elsewhere or who were treated initially with a different method were excluded from the study, as were patients who had a teratologic or neuromuscular dislocation, or those who had inadequate radiographs and clinical records. Patients who discontinued brace treatment due to poor compliance or some complications were also excluded.

The Pavlik harness was applied by 16 trained pediatric orthopaedists with the hip flexed to 90 to 100 degrees. The posterior straps were lax enough for the knees to come to the midline in the position of hip flexion. Reduction was confirmed by palpation and radiography before the introduction of ultrasonography. Ultrasonographic screening through an anterior approach and clinical and radiologic examinations has been added for the assessment of reduction since 1991. Spontaneous reduction usually occurred within 1 or 2 weeks after the application of the harness. The patients were checked every few days during the first 2 weeks until reduction was achieved. After reduction, the patients were examined every 2 weeks for 1 or 2 months and then every 4 weeks thereafter. No additional braces were used after the Pavlik harness treatment. If reduction could not be obtained or maintained within the first 2 to 3 weeks, the harness was discontinued and overhead traction was attempted.

Three patients discontinued harness treatment due to noncompliance by the parents. Two infants were obliged to remove the brace within a few days after an application of the harness because they were in bad humor (crying bitterly) and would not take sufficient milk. Finally, 221 hips of 210 patients (31 subluxations and 190 dislocations) met the criteria for inclusion in the study. Patient demographics were reviewed for generally accepted risk factors influencing the outcome of Pavlik harness treatment; sex, bilaterality, side of pathology, age at the time of initiation of harness treatment, degree of adduction contracture, reducibility (Ortolani-positive), family predisposition, and duration of Pavlik harness treatment. Adduction contracture of the hip, which was evaluated on the basis of passive abduction with the hips flexed to 90 degrees, were classified into 2 groups according to maximal abduction (abduction ≥ 60 degrees: good ABD group, abduction < 60 degrees: poor ABD group). The radiographs were taken in the supine position, with both lower extremities extended in a neutral position between external and internal rotation, and the tube distance was 1 m. The severity of dislocation was measured on a plain anteroposterior radiograph taken before initial treatment according to the method of Yamamuro and Chene[19] (Fig. 1). The distance between the midpoint of the proximal metaphyseal border of the femur and the Hilgenreiner line was termed distance *a*. The distance between the midpoint of the proximal metaphyseal border of the femur and the line that is adjacent to the lateral border of the ischium was termed distance *b*. Thus, the amount of proximal displacement was represented by distance *a*, and that of lateral displacement by distance *b*. The presence of AVN was diagnosed according to the criteria of Salter et al[20]: (1) failure of the appearance of the ossific nucleus of the femoral head during 1 year or longer after reduction; (2) failure of growth in an existing ossific nucleus during 1 year or longer after reduction; (3) broadening of the femoral neck during 1 year after reduction; (4) increased radiographic density of the femoral head followed by the radiographic appearance of fragmentation; and (5) residual deformity of the femoral head and neck when reossification is complete. Severity of AVN was classified by the method of Kalamchi-MacEwen.[14]

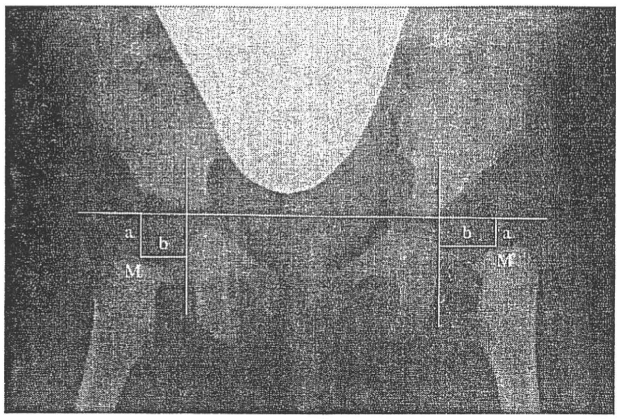

FIGURE 1. A plain anteroposterior radiograph taken before initial treatment. The letter M marks the middle point of the proximal metaphyseal border of the femur. Distance *a* represents the distance between M and the Hilgenreiner line, and distance *b* represents the distance between M and the line that is adjacent to the lateral border of the ischium.

First, univariate analysis was performed between the successes and the failures of reduction to assess the differences with regard to sex, laterality, side of pathology, age at initiation of harness treatment, severity of dislocation before treatment (distance *a* and distance *b*), degree of adduction contracture, reducibility, and family predisposition. Next, the incidence of AVN after reduction by the Pavlik harness was binary-coded and univariate analysis was also performed between AVN (+) and AVN (−) to assess the differences regarding the above variables and the duration of harness treatment. Continuous variables were compared by the

nonparametric Mann-Whitney U test and categorical variables by the Fisher exact test or the Pearson test, where appropriate. Finally, independent multivariate predictors of outcome were identified using logistic regression in which all variables with a P value of less than 0.20 from the univariate analysis were entered into the stepwise model for the selection of the explanatory variables. The likelihood ratio by using the χ^2 test was used to determine the significance of each predictor or possible 2-way interactions among variables. Significant predictors of outcome were analyzed by calculating the odds ratio of maximal likelihood with 95% confidence intervals (CI). A P value of less than 0.05 was considered statistically significant. Data analysis was performed using JMP version 6 (SAS Institute, Cary, NC).

RESULTS

Overall Results of the Pavlik Harness Treatment (Table 1)

One hundred and ninety patients were female (90.5%) and 20 were male (9.5%). One hundred and thirty-five (61.1%) of 221 DDH were on the left and 64 hips (28.9%) were on the right. Eleven patients had bilateral hip involvement. The average age at the initiation of harness treatment was 3.9 ± 1.08 months. Distance *a* and distance *b* before Pavlik harness treatment was averaged 7.4 ± 2.38 and 11.6 ± 2.07 mm, respectively. Range of hip abduction was recorded in 202 of 221 hips. Good ABD group comprised 132 hips (65%) and poor ABD 70 hips (35%). Thirty-nine hips (18%) were reducible by the Ortolani maneuver (Ortolani-positive) whereas there were 182 (82%) Ortolani-negative hips. One-third of the patients had a familial predisposition. One hundred and eighty-one hips were reduced with the Pavlik harness and average duration of total harness treatment was 112 ± 22.3 days (full-time bracing in 165 hips and part-time wear followed by full-time bracing in 16 hips). The overall rate of reduction was 81.9%. In 1 patient with bilateral DDH, one hip was reduced in the harness and the other was not. The hips that were unreduced with the Pavlik harness were subsequently treated by overhead traction, and all hips were finally reduced conservatively. AVN of the femoral head was identified in 16 of the 181 reduced hips (8.8%) according to the criteria of Salter et al.[20] There were 3 hips in grade 1, 4 hips in grade 2, 5 hips in grade 3, and 4 hips in grade 4 classified by the method of Kalamchi-MacEwen.[14]

Predictive Factors for the Failure of Reduction (Tables 2, 4)

Sex did not correlate with the failure of reduction in Pavlik harness treatment in univariate analysis ($P = 0.1045$). The reduction rate was 70% in male and 82.9% in female patients.

Bilaterality was associated with an increased risk of Pavlik harness failure both in univariate ($P = 0.0002$) and multivariate ($P = 0.0182$) analyses. Of the 199 hips with unilateral DDH, only 29 hips (15%) failed Pavlik harness treatment whereas 11 of the 22 hips (50%) with bilateral involvement eventually failed. The estimated odds ratio of failure was approximately 6 times higher for the patients with bilateral DDH than for those that were unilaterally affected (odds ratio 5.9, 95% CI = 2.3–14.8).

Within the narrow range of ages of infants treated by the Pavlik harness in this study, there was no statistically significant relationship between age and likelihood of failure ($P = 0.0559$). The average age at initial treatment for successfully reduced hips and for unreduced hips was 3.93 and 3.63 months, respectively.

In univariate analysis, the average distance *a* before treatment was significantly greater in the reduced hips than in the unreduced hips (7.95 ± 2.04 vs. 5.07 ± 2.37 mm) ($P < 0.0001$). Similarly, the average distance *b* of the reduced hips (11.2 ± 1.96 mm) was significantly smaller than that of the unreduced hips (13.1 ± 1.87 mm) ($P < 0.0001$). Distance *a* was the most powerful predictor for failed reduction in multivariate analysis ($P = 0.0002$). Distance *b*, in contrast, was not a significant multivariate predictor for the failure of reduction in Pavlik harness treatment ($P = 0.0719$).

Reduction was obtained in 115 hips with the good ABD group (87%) and in 49 hips with the poor ABD group (69%). Adduction contracture of the hip was a prognostic factor for the failure of reduction in univariate

TABLE 1. Categorical and Continuous Variables for the Outcome of the Pavlik Harness Treatment

Categorical Variables	No. Hips (Patients)
Male/female	20/190
Right/left/bilateral	64/135/22
Good ABD/poor ABD	132/70
Reducible/irreducible	39/182
Family predisposition (+/−)	74/147
Continuous Variables	**Mean ± SD**
Age at initial treatment	3.9 ± 1.08 mo
Distance *a*	7.4 ± 2.38 mm
Distance *b*	11.6 ± 2.07 mm
Duration of bracing	112 ± 22.3 d

TABLE 2. Univariate Analysis for the Failure of Reduction by the Pavlik Harness Treatment

	Reduction (+)	Reduction (−)	*P*
No. hips	181	40	
Sex (F/M)	165/16	33/7	0.1045
Laterality (L + R/B)	170/11	29/11	0.0002*
Age at treatment (mo)	3.93 ± 1.10	3.63 ± 1.03	0.0559
Distance *a* (mm)	7.95 ± 2.04	5.07 ± 2.37	< 0.0001*
Distance *b* (mm)	11.2 ± 1.96	13.1 ± 1.87	< 0.0001*
Abduction (good/poor)	115/49	17/21	0.0003*
Reducibility (±)	36/145	3/37	0.0629
Family predisposition (+/−)	56/125	18/22	0.0881

Continuous variables are expressed as the mean ± standard deviation.
*Statistically significant.

TABLE 3. Univariate Analysis for the Incidence of AVN by the Pavlik Harness Treatment

	AVN (+)	AVN (−)	*P*
No. hips	16	165	
Sex (F/M)	15/1	150/15	0.7023
Laterality (L+R/B)	14/2	156/9	0.5185
Age at treatment (mo)	3.88 ± 0.72	3.94 ± 1.13	0.9135
Distance *a* (mm)	6.89 ± 1.86	8.05 ± 2.03	0.0209*
Distance *b* (mm)	12.0 ± 1.98	11.2 ± 1.95	0.0694
Abduction (good/poor)	5/10	110/39	0.0011*
Reducibility (±)	5/11	31/134	0.2331
Family predisposition (±)	6/10	50/115	0.5521
Duration of bracing	112 ± 8.44	113 ± 23.1	0.9623

Continuous variables are expressed as the mean ± standard deviation.
*Statistically significant.
AVN indicates avascular necrosis.

analysis ($P = 0.0003$). Nonetheless, it was not a significant multivariate predictor ($P = 0.1097$).

One hundred and forty-five of the 182 Ortolani-negative hips (80%) were reduced by the Pavlik harness whereas 3 Ortolani-positive hips were not stabilized by the harness treatment. As a result, irreducibility was not a significant univariate predictor for the failure of reduction ($P = 0.0629$) although it correlated with failed reduction in multivariate analysis ($P = 0.0340$).

Family predisposition did not correlate with failure of reduction in univariate analysis ($P = 0.0881$).

Predictive Factors for the Incidence of AVN (Tables 3, 4)

No significant difference was found between the AVN (+) and AVN (−) groups with respect to sex, laterality, side of pathology, age at initial treatment, distance *b*, reducibility, family predisposition, and duration of bracing. Distance *a* averaged 6.89 ± 1.86 mm in the AVN (+) group and 8.05 ± 2.03 mm in the AVN (−) group, which correlated with an increased likelihood of AVN in univariate analysis ($P = 0.0209$). In multivariate analysis, however, decreased distance *a* was not a significant predictor for the incidence of AVN ($P = 0.0988$). In contrast, adduction contracture of the hip was a significant univariate ($P = 0.0011$) and multivariate ($P = 0.0019$) risk factor for the incidence of AVN. AVN of the femoral head occurred in 10 of the 49 hips with the poor ABD group (20.4%) and in 5 of the 115 hips with the good ABD group (4.3%). The estimated odds ratio of AVN occurrence was more than 5 times higher for the hips with poor ABD than for those with good ABD (odds ratio 5.6, 95% CI = 1.8–17.5).

TABLE 4. Multivariate Predictors of the Outcome by the Pavlik Harness Treatment

	Variables	*P*
Reduction	Laterality	0.0182*
	Age at treatment	0.1653
	Distance *a*	0.0002*
	Distance *b*	0.0719
	Abduction	0.1097
	Reducibility	0.0340*
AVN	Distance *a*	0.0988
	Abduction	0.0019*

*Statistically significant.

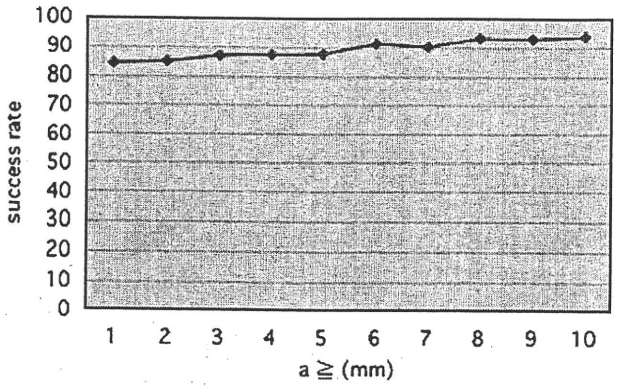

FIGURE 2. The graph represents changes in the success rate of the good ABD group for cumulative increment of distance a. More than 90% of the success rate was demonstrated when distance *a* increased to 6 mm or greater.

Our results show that decreased distance *a* was the most powerful predictor of the failure of reduction, and severe adduction contracture of the hip (poor ABD group) was the most reliable risk factor for the incidence of AVN in the treatment of the Pavlik harness. Then, we examined the outcome of Pavlik harness treatment by focusing on these 2 variables. The hips that were reduced without AVN were determined as successful treatment and the hips that were reduced followed by AVN or those that were unreduced as unsuccessful treatment. The overall success rate was 74.7% (165 of 221) in this series. Figure 2 showed the changes in the success rate of the good ABD group (minimal adduction contracture) as increasing distance *a*. The rate of successful treatment with the Pavlik harness increased up to 91.2% when the good ABD group had distance *a* of 6 mm or greater.

DISCUSSION

This study examined a sufficient number of DDH treated with the Pavlik harness and analyzed the correlative factors to treatment failure statistically. We believe our results provided important implications for safe and useful application of Pavlik harness treatment for DDH. There are, however, some limitations in this study mainly because of its retrospective nature. First, the hips in this series included not only developmental dislocations but also subluxations, the results of which would be superior to those of dislocations. Second, intraobserver and interobserver reliability of the radiographic measures (Yamamuro's *a* and *b*) and clinical measures (adduction contracture of the hip) has not been tested. Third, the duration in the harness for successfully reduced hips is a subjective decision, which may be biased by the physicians. The harness was worn full time during the course of treatment in some patients, whereas others

had part-time bracing followed by full-time bracing. In addition, actual compliance and use of the harness in the home were impossible to determine reliably in a retrospective study.

Various investigators confirmed the effectiveness of ultrasonography in evaluating the severity of dislocation and diagnosing DDH.[7,8,10–12,17,18,21,22] Suzuki et al[23] reported that the patients whose hips were posteriorly dislocated on a transverse ultrasonography view uniformly failed the Pavlik harness treatment. Ultrasonography, which allows visualization of the cartilaginous components of the acetabulum and femoral head that are not distinguishable on routine radiographs, is a noninvasive and effective method, but it needs a specialist and it may not be available in all institutes. In contrast, distance *a* and distance *b*, which can be easily measured before the appearance of the ossification center of the femoral head, are constant up to 4 years of age and influenced very little by positional changes of the limb.[19] The usefulness of measuring distance *a* has been widely documented in Japan.[5,9] This method is more practical because it can be performed in any medical institute. Thus, we used these measures in evaluating the severity of DDH in this study.

Several investigators have reported various risk factors for the failure of reduction by the Pavlik harness treatment including male sex,[14] advanced age at the time of Pavlik harness initiation,[7,9,16,18] bilaterality,[10,16] and severity of dislocation.[5,9,10,17] In this study, similar to the Lerman et al[10] series, sex and age at initial treatment did not correlate with failure of reduction. The age groups of their study, however, were not compatible with those of our study. The average age at initial treatment of this study (3.9 mo) was older than that of their series (7 d). This is because the majority of patients were referred to us for clinical signs such as limited abduction, shortening of the affected extremity, or positive click sign after routine pediatric screening programs at the age of 3 months. The results of this study may not be generalizable to DDH infants less than 3 months of age.

Distance *b* and adduction contracture of the hip were univariate risk factors for the failure of reduction but not multivariate risk factors. Bilaterality and decreased distance *a* were univariate and multivariate predictors for failed reduction by Pavlik harness treatment. Lerman et al[10] and Viere et al[16] showed a statistically increased likelihood of failure of Pavlik harness treatment in patients with bilateral involvement, whereas Harding et al[18] and Hangen et al[7] found that bilaterality did not correlate with Pavlik harness failure. Patients with bilateral DDH, in our series, were approximately 6 times as likely to fail Pavlik harness treatment as were those with unilateral DDH. This study, however, showed that decreased distance *a* was the most powerful statistical predictor for the failure of reduction. Suzuki and Yamamuro[5] reported that the rate of reduction was 97% when distance *a* was greater than 4 mm, whereas the rate of reduction decreased to 61% when distance *a* was less than 4 mm. Inoue et al[9] described that distance *a* of 7 mm or smaller is a risk factor for unsuccessful reduction. These studies and the present one documented an increasing likelihood of failure of Pavlik harness treatment with increasing proximal displacement of the femur, which may also indicate stiffness of soft tissues around the hip such as a tight iliopsoas.

A hip reduced using the Pavlik harness followed by AVN, which often leads to subsequent deformity of the femoral head, is difficult to treat. Therefore, treatment with the Pavlik harness should be done carefully to prevent the development of AVN. There is a debate in the orthopaedic literature with regard to the reduction of the hip in DDH before the appearance of an ossific nucleus. Some orthopaedists believe that the ossific nucleus of femoral head has a protective effect, which decreases the risk of iatrogenic ischemic injury to the femoral head during reduction, and that the treatment of DDH should be delayed until its development.[20,24] In this series, however, the incidence of AVN with the use of the Pavlik harness was not dependent on age at initial application, although the age group of this study was relatively old. Suzuki and Yamamuro[5] showed that the incidence of AVN rose as distance *a* decreased and concluded that the more severe the dislocation, the higher the rate of AVN as a complication of treatment with the Pavlik harness. In this study, decreased distance *a* was a univariate risk factor for the incidence of AVN, but not a multivariate risk factor, unlike in the Suzuki and Yamamuro series. In contrast, the pretreatment adduction contracture of the hip was a univariate and multivariate risk factor for the incidence of AVN. Several investigators suggested that excessive abduction of the hip, such as tightening of the posterior strap, may result in AVN.[1,20,25,26] Ramsey et al[1] termed the safe zone, which is defined as the arc between the angle of abduction that can be comfortably attained and the angle that allows redislocation. The safe zone is extremely narrow when pretreatment contracture of soft tissue limits abduction markedly. As a result, there may be greater risk of AVN by relatively too much abduction beyond the safe zone when reduction occurred in the hips with severe adduction contracture.

Satisfactory outcome by the Pavlik harness treatment was shown in the DDH with an abduction of ≥ 60 degrees (flexed to 90 degrees) and distance $a \geq 6$ mm. We concluded that the Pavlik harness is a very safe and effective means of initial treatment of DDH for these hips. For the treatment of DDH in which distance *a* was less than 6 mm or maximal abduction was less than 60 degrees, additional treatment should be considered before the application of the Pavlik harness to decrease the proximal displacement of the femur and to relieve soft tissue contractures around the hip.

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