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Clinical Article

The Impact of Menopause on Bone Fusion after the Single-Level Anterior Cervical Discectomy and Fusion

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Objective : To evaluate the successful fusion rate in postmenopausal women with single-level anterior cervical discectomy and successful fusion (ACDF) and identify the significant factors related to bone successful fusion in pre- and postmenopausal women.
Methods : From July 2004 to December 2010, 108 consecutive patients who underwent single-level ACDF were prospectively selected as candidates. Among these, the charts and radiological data of 39 women were reviewed retrospectively. These 39 women were divided into two groups : a premenopausal group (n=11) and a postmenopausal group (n=28). To evaluate the significant factors affecting the successful fusion rate, the following were analyzed : the presence of successful fusion, successful fusion type, age, operated level, bone mineral density, graft materials, stand-alone cage or plating with autologous iliac bone, subsidence, adjacent segment degeneration, smoking, diabetes mellitus, and renal disease.
Results : The successful fusion rates of the pre- and postmenopausal groups were 90.9% and 89.2%, respectively. There was no significant difference in the successful fusion rate or successful fusion type between the two groups. In the postmenopausal group, three patients (10.8%) had successful fusion failure. In the postmenopausal group, age and subsidence significantly affected the successful fusion rate (p=0.016 and 0.011, respectively), and the incidence of subsidence in patients with a cage was higher than that in patients with a plate (p=0.030).
Conclusion : Menopausal status did not significantly affect bone successful fusion in patients with single-level ACDF. However, in older women with single-level ACDF, the combination of use of a cage and subsidence may unfavorably affect successful fusion.

Key Words : Menopause · Cervical · Discectomy · Successful fusion · Bone mineral density.

INTRODUCTION

Estrogen is a primary regulator of ovarian function and affects bone health in women[5,15]. Estrogen has a positive effect on bone homeostasis by increasing preosteoblast proliferation and inhibiting osteoclastogenesis[6,13,14,17]. However, after menopause the loss of ovarian function, including the withdrawal of estradiol, has an impact on the female skeleton[10,15]. Because the loss of estrogen results in a negative bone remodeling, rapid bone loss occurs during the first 5-10 years after menopause[11,16]. The perimenopausal period usually occurs in a woman's late forties and early fifties. Bone loss accelerates during late perimenopause and continues in the postmenopausal period[4]. The negative bone remodeling causes attenuation of microstructure of bone. Therefore, postmenopausal women over 50 years of age who need to undergo spine surgery may have negative bone metabolism and there may have a poor rate of successful fusion after spine surgery.

Previous reports indicate that more than half of the patients who undergo spine surgery are 50 years old, and that about 70% of the women who undergo spine surgery have osteopenia or osteoporosis[2]. The studies reported the successful fusion rate with lumbar arthrodesis in osteoporotic patients to be 89.7% and 95.8%[1,9]. The studies suggest that osteoporosis is not an absolute contraindication for spinal arthrodesis. However, it is true that osteoporosis is associated with a poor successful fusion rate and poor bone stability[16]. There are many strategies to overcome the effect of osteoporosis on bone successful fusion in osteoporotic patients who need spine surgery[3,12,14]. However, some postmenopausal women are not osteoporotic and the

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percentage of women undergoing spine surgery who are osteopenia was reported to be 30%[2]. Because nonosteoporotic postmenopausal women may have negative bone metabolism, clarification of the effect of menopause on bone successful fusion is necessary. However, to our knowledge, there has been no study of the effects of menopause on spine successful fusion. Therefore, we evaluated bone successful fusion in postmenopausal patients undergoing single-level anterior cervical discectomy and fusion (ACDF).

MATERIALS AND METHODS

Patients

For a comparison between stand-alone cage and anterior plating procedures in single-level cervical disc disease, we prospectively recruited the patients undergoing single-level ACDF using a cage or an anterior plate from July 2004 to December 2010. One-hundred-eight patients consented to participate in the study. Of these, we enrolled in the present study 39 women who had at least a 12-month follow-up period after ACDF and performed retrospective chart and radiological reviews. We divided the patients into two groups, premenopausal and postmenopausal, to compare the bone successful fusion in these two groups. There were 11 premenopausal and 28 postmenopausal patients. Because the acceleration of bone loss begins in the late perimenopausal period, patients aged 55 years and older were allocated to the postmenopausal group and patients less than 50 years old were allocated to the premenopausal group. To reduce the bias of perimenopause status, the patients from 50 years to 54 years were excluded in this study. Therefore, the mean ages of the premenopausal and postmenopausal groups were 45.27±9.056 years and 63.64±7.602 years, respectively. Because the patients with a bone mineral density (BMD) T-score of -3 or less in the lumbar spine were excluded from the prospective study, the ratio of patients in the postmenopausal group with normal bone density to those with osteopenia to those with osteoporosis was 7 : 11 : 4 (p=0.004). However, there was still a significant difference between the two groups in the lumbar spine BMD (p=0.027). There was no significant difference in operated level, graft materials (autologous bone or allogenic bone), frequency of taking an osteoporotic drug, diabetes mellitus, or renal disease. There were two smokers in the premenopausal group and none in the postmenopausal group (p=0.021) (Table 1).

Operative technique

All patients were operated on using the standard Smith-Robinson approach followed by neural decompression[20]. The anterior plate (Blackstone, Medical Inc., Springfield, MA, USA or Atlantis®, Medtronic Sofamor Danek, Minneapolis, MN, USA) or cage (MC+®, LDR Medical France, Solis®, Stryker, Kalamazoo, MI, USA) procedures were randomly selected. The cage was filled with allogenic or Autologous bone. When using an anterior plate procedure, harvesting tricortical iliac bone was inserted into the disc space followed by anterior plating.

Outcome assessment

The primary purpose of this study was the comparision of the successful fusion rate in the two groups. The definition of successful fusion was the presence of bridging bone in the disc space or anterior or posterior vertebral corner (Fig. 1). The secondary purpose was to identify the significant factors affecting the bone successful fusion in pre- and postmenopausal women. The factors considered were age, operated level, BMD, graft materials, stand-alone cage, plating with autologous iliac bone, subsidence, adjacent segment degeneration (ASD), smoking, diabetes mellitus, and renal disease. The cage or grafted bone was sunk into adjacent vertebral body was indicated the subsidence. The development of new spondylotic changes in the adjacent vertebral bodies or a decrease of more than 10% in the height of the adjacent discs was considered to indicate ASD. The patients' charts and radiological images were reviewed to accomplish the primary and secondary purposes.

Statistical analysis

Statistical analyses were performed using commercially available SPSS software, version 20.0 (IBM SPSS Inc., Armonk, NY, USA). To compare pre- and postmenopausal groups and the relationships between the different factors and successful fusion in the

Table1. Demographic data of women underwent single-level ACDF

	PreM (n=11)	PostM (n=28)	p value	
Follow up period (months)	42.27±3.344	29.57±13.147	0.005	t-test
BMD (T-score in lumbar spine)	0.90±0.565	-1.32±1.277	0.027	t-test
Operated level			0.328	Fisher's exact test
C3-4	0	1		
C4-5	1	5		
C5-6	9	14		
C6-7	1	8		
Cage : Plate	8 : 3	18 : 10	0.615	Fisher's exact test
Grafted materials (Autograft : Allograft)	2 : 9	9 : 19	0.383	Fisher's exact test
Anti-osteoporotic drug	0	2	0.837	Fisher's exact test
Smoking	2	0	0.021	Fisher's exact test
Diabetes mellitus	0	7	0.067	Fisher's exact test
Renal disease	0	0		

PreM : premenopause, PostM : postmenopause, BMD : bone mineral density, ACDF : anter cervical discectomy and successful fusion

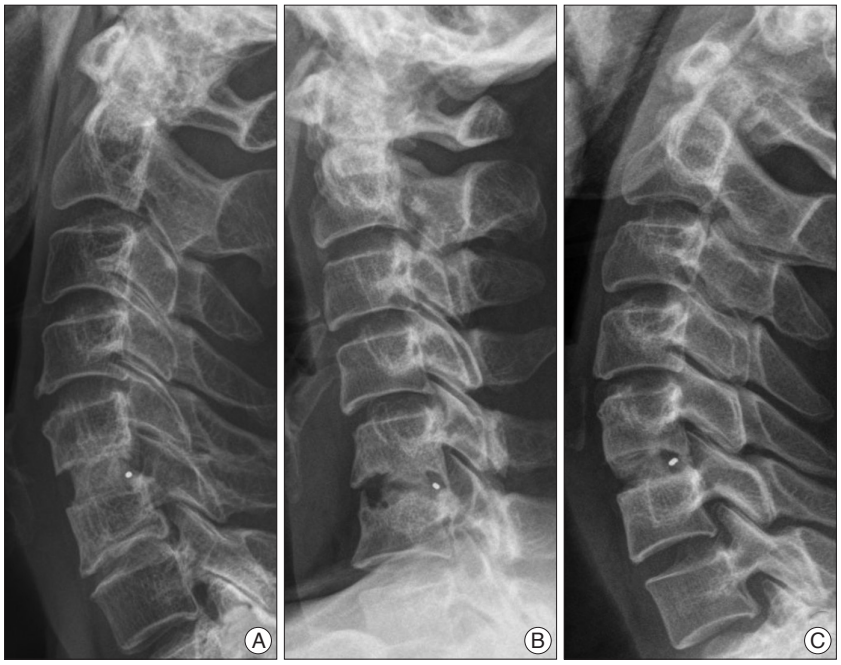

Fig. 1. Plain X-rays show the examples of successful fusion in different site after ACDF. A : Successful fusion with a bridging bone in disc space. B : Successful fusion with a bridging bone in posterior corner. C : Successful fusion with bridging bones in disc space and posterior corner. ACDF : anterior cervical discectomy and successful fusion.

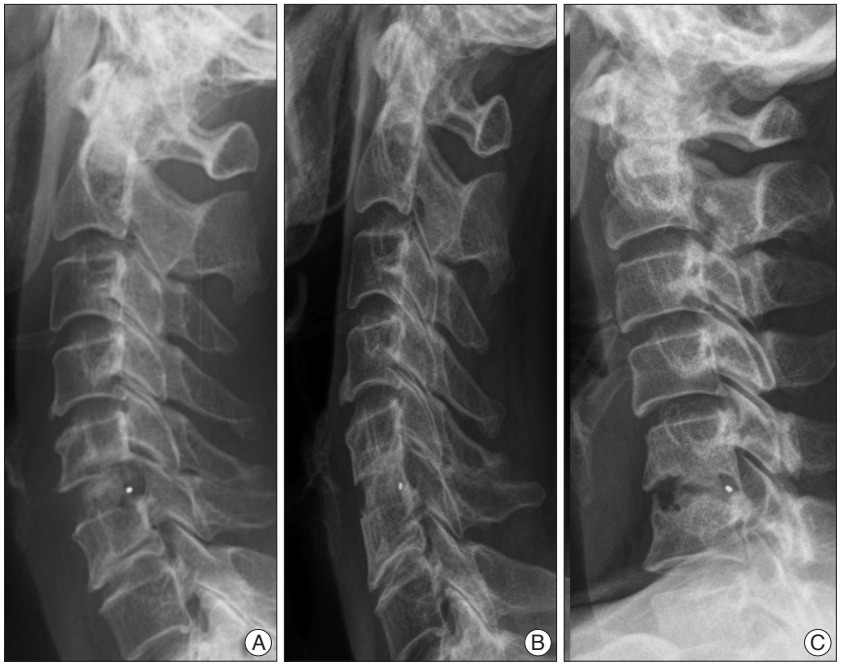

Fig. 2. Plain X-rays show the examples of adjacent segment degeneration and subsidence after ACDF. A : Immediate postoperative X-ray. B : Increased body spur at superior adjacent level at 12 month after surgery. C : Subsidence is shown at the fused segment using cage. ACDF : anterior cervical discectomy and successful fusion.

postmenopausal group, a two-sample Student's t-test was used to compare continuous values and Pearson's chi-square or Fisher's exact test was used for categorical values. Two-sided p values <0.05 were assumed to be significant.

RESULTS

Comparison between pre- and postmenopausal groups

In the premenopausal group, 10/11 (90.9%) patients showed successful fusion after ACDF, as did 25/28 patients (89.2%) in the postmenopausal group. There was no significant difference in the successful fusion rate between the two groups (p=0.880). With respect to the locations of bridging bone (disc space or vertebral corner), bone formation in the disc space was dominant in both groups (80% vs. 48%, p=0.224). The incidence of subsidence in the pre- and postmenopausal groups was 27.2% (3/11) and 25% (7/28), respectively; this difference was not significant (p=0.884). There was no significant difference between the two groups in the incidence of ASD (54.5% vs. 42.8%, p=0.510) (Fig. 2A, B).

Significant factors related to successful fusion in postmenopausal patients

Among the factors considered, including age, operated level, BMD, graft materials, cage or plate procedure, subsidence, ASD, smoking, diabetes mellitus, and renal disease, only age and subsidence significantly affected the successful fusion rate (p=0.016 and 0.011, respectively) (Fig. 2C). There were 25 patients with successful fusion and three without successful fusion. The mean age of patients with successful fusion was 62±6.0 and non-union was 73±13.5 years. Although all patients non-union had subsidence, four patients (16%, 4/25) with successful fusion also had subsidence (Table 2).

Comparison of patients with stand-alone cage and plating with autologous iliac bone

Among patients with a plate (n=13), there was no subsidence. However, there were 10 patients with cage who had subsidence (38.4%, 10/26). The incidence of subsidence at cage group was significantly higher than that of plating group (p=0.010). The incidence of ASD in patients with a cage was 38.4% (10/26), and in

those with a plate it was 62.5% (8/13). However, this difference was not significant. In the postmenopausal group, the incidence of subsidence in patients with a cage was 36.8% (7/18), and it was 0% (0/10) in those with a plate, a difference of that was significant (p=0.030). However, the difference in the incidence of ASD between the groups was not significant (p=0.243) (Table 2).

DISCUSSION

The purposes of the present study were to identify the effect of estrogen deficiency on spine successful fusion by evaluation the successful fusion rate in pre- and postmenopausal patients after single-level ACDF, and to investigate the factors associates with successful fusion. The results indicate that there was no significant difference in the successful fusion rate between pre- and postmenopausal patients, and the factors that had a significant influence on successful fusion were age and subsidence. Subsidence occurred more frequently in patients with a cage than in patients with a plate, regardless of their menopausal status.

Effect of estrogen deficiency on bone successful fusion

Although patients with severe osteoporosis (T-score <-3) were excluded from this prospective study, three osteoporotic patients were included. Therefore, it is not reasonable to discuss the effect of estrogen deficiency with the osteoporosis on bone successful fusion based on the present study. However, the difference in BMD between the pre- and postmenopausal groups was significant (p=0.027), which suggests that in our study, the postmenopausal patients had the lower bone metabolism than the premenopausal patients. Menopause-related estrogen deficiency leads to reduce bone formation[19]. In the present study, the mean T-score for BMD of the postmenopausal group was at the level of osteopenia (-1.32±1.277). It was previously reported that the incidence of osteopenia in patient undergoing spine surgery was 40.4%, 41.5%, and 68.1% in patients' aged 50-59, 60-69, and 70-79 years, respectively[2]. Therefore, it may be valuable to evaluate the effects of postmenopausal status on spine successful fusion. Although menopause-related estrogen deficiency without osteoporosis decreases bone quality, it may not have significantly hindered single-level cervical successful fusion in postmenopausal women compared with premenopausal women.

Subsidence in anterior cervical successful fusion

The incidence of cage subsidence has been reported to vary from 19% to 62%[4,7,18,21]. Although subsidence was not significantly correlated with clinical outcome, there was a significant positive relationship between non-union and subsidence[21,22]. In the present study, subsidence was significantly associated with non-union (p=0.011). The subsidence can induce the decrease of the disc height at operated level, and this narrowed disc space may indicate a decrease in the space that needs to be filled with bridging bone. Therefore, an increased incidence of subsidence could be predicted to be associated with an increased successful fusion rate. However, several studies, including this one, show a negative relationship between subsidence and successful fusion[21,22]. The persuasive explanation is that subsidence causes the deterioration of local and overall cervical alignment; thus the potential advantage for bone successful fusion of a narrowed disc space after subsidence cannot overcome the detrimental effect of the deterioration of local and overall cervical alignment[22].

The present study has some limitations. To evaluate the primary and secondary outcomes of this study, we retrospectively used the information from a prospective randomized study, the purpose of which was to compare the sagittal alignment between a stand-alone cage and plating with autologous iliac bone[8]. Therefore, because of the small number of patients who were enrolled in the present study, we cannot draw a strong conclusion in terms of whether menopause is a significant factor in bone successful fusion after the single-level ACDF. The criteria for dividing two groups were obvious in the present study. Therefore, osteopenia, osteoporosis, BMD and estrogen study should be considered in the future study. Although the postmenopausal group which had the shorter follow-up duration had the similar successful fusion rate, the difference of follow-up duration between two groups was significant. And, the bias related with aging was not excluded in the present study. In addition, the present study does not involve multilevel anterior cervical successful fusion. Because menopause can negatively affect bone remodeling, it could hinder bone successful fusion in a multilevel cervical successful fusion. Therefore, further prospective investigations with a large

Table 2. The comparison of postmenopausal patients with or non-union

	Successful fusion (n=25)	Non-union (n=3)	p value	
Age (years)	62±6.0	73±13.5	0.016	t-test
BMD (T-score in lumbar spine)	-1.03±1.576	-0.46±1.069	0.556	t-test
Follow-up period (months)	30.6±13.37	20.3±6.65	0.203	t-test
Cage : Plate	15 : 10	3 : 0	0.172	Fisher's exact test
Allbone : Autograft	16 : 9	3 : 0	0.530	Fisher's exact test
Subsidence (%)	4 (16)	3 (100)	0.011	Fisher's exact test
ASD (%)	10 (40)	2 (66.6)	0.560	Fisher's exact test
Cage : Plate	8 : 3	18 : 10	0.615	Fisher's exact test
Anti-osteoporotic drug	2	0	1.000	Fisher's exact test
Smoking	0	0		
Diabetes mellitus	5	2	0.560	Fisher's exact test
Renal disease	0	0		

BMD : bone mineral density, ASD : adjacent segment degeneration

sample size, including single and multiple level successful fusions, are required to evaluate more precisely the correlation between osteopenia and osteoporosis related to estrogen deficiency and the bone successful fusion process following cervical successful fusion surgery. Menopause-related estrogen deficiency did not significantly affect bone successful fusion in patients with single-level ACDF. However, older women who undergo single-level ACDF with a cage that subsides may have a risk of successful fusion failure.

CONCLUSION

Menopausal status with estrogen deficiency did not significantly affect successful fusion in patients with single-level ACDF. The subsidence in the patients with cage frequently occurred than that of patients with plate. And, if the older women underwent the single-level ACDF, the combination of use of a cage and subsidence may unfavorably affect successful fusion.

References

1. Cavagna R, Tournier C, Aunoble S, Bouler JM, Antonietti P, Ronai M, et al. : Lumbar decompression and fusion in elderly osteoporotic patients : a prospective study using less rigid titanium rod fixation. **J Spinal Disord Tech 21** : 86-91, 2008
2. Chin DK, Park JY, Yoon YS, Kuh SU, Jin BH, Kim KS, et al. : Prevalence of osteoporosis in patients requiring spine surgery : incidence and significance of osteoporosis in spine disease. **Osteoporos Int 18** : 1219-1224, 2007
3. Ferguson SJ, Winkler F, Nolte LP : Anterior fixation in the osteoporotic spine : cut-out and pullout characteristics of implants. **Eur Spine J 11** : 527-534, 2002
4. Gercek E, Arlet V, Delisle J, Marchesi D : Subsidence of stand-alone cervical cages in anterior interbody fusion : warning. **Eur Spine J 12** : 513-516, 2003
5. Hadji P, Coleman R, Gnant M, Green J : The impact of menopause on bone, zoledronic acid, and implications for breast cancer growth and metastasis. **Ann Oncol 23** : 2782-2790, 2012
6. Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Spelsberg TC, Riggs BL : Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. **Endocrinology 140** : 4367-4370, 1999
7. Kast E, Derakhshani S, Bothmann M, Oberle J : Subsidence after anterior cervical inter-body fusion. A randomized prospective clinical trial. **Neurosurg Rev 32** : 207-214; discussion 214, 2009
8. Kim CH, Chung CK, Hahn S : Autologous iliac bone graft with anterior plating is advantageous over the stand-alone cage for segmental lordosis in single-level cervical disc disease. **Neurosurgery 72** : 257-265; discussion 266, 2013
9. Kim KH, Lee SH, Lee DY, Shim CS, Maeng DH : Anterior bone cement augmentation in anterior lumbar interbody fusion and percutaneous pedicle screw fixation in patients with osteoporosis. **J Neurosurg Spine 12** : 525-532, 2010
10. Lo JC, Burnett-Bowie SA, Finkelstein JS : Bone and the perimenopause. **Obstet Gynecol Clin North Am 38** : 503-517, 2011
11. Manolagas SC, Jilka RL : Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. **N Engl J Med 332** : 305-311, 1995
12. McNulty CA, Bowen J, Foy C, Gunn K, Freeman E, Tompkins D, et al. : Urinary catheterization in care homes for older people : self-reported questionnaire audit of catheter management by care home staff. **J Hosp Infect 62** : 29-36, 2006
13. Nelson ER, DuSell CD, Wang X, Howe MK, Evans G, Michalek RD, et al. : The oxysterol, 27-hydroxycholesterol, links cholesterol metabolism to bone homeostasis through its actions on the estrogen and liver X receptors. **Endocrinology 152** : 4691-4705, 2011
14. Nelson ER, Wardell SE, McDonnell DP : The molecular mechanisms underlying the pharmacological actions of estrogens, SERMs and oxysterols : implications for the treatment and prevention of osteoporosis. **Bone 53** : 42-50, 2013
15. Nicks KM, Fowler TW, Akel NS, Perrien DS, Suva LJ, Gaddy D : Bone turnover across the menopause transition : The role of gonadal inhibins. **Ann N Y Acad Sci 1192** : 153-160, 2010
16. Park SB, Chung CK : Strategies of spinal fusion on osteoporotic spine. **J Korean Neurosurg Soc 49** : 317-322, 2011
17. Scheven BA, Damen CA, Hamilton NJ, Verhaar HJ, Duursma SA : Stimulatory effects of estrogen and progesterone on proliferation and differentiation of normal human osteoblast-like cells in vitro. **Biochem Biophys Res Commun 186** : 54-60, 1992
18. Schmieder K, Wolzik-Grossmann M, Pechlivanis I, Engelhardt M, Scholz M, Harders A : Subsidence of the wing titanium cage after anterior cervical interbody fusion : 2-year follow-up study. **J Neurosurg Spine 4** : 447-453, 2006
19. Seeman E : Lancet. Pathogenesis of bone fragility in women and men. **Lancet 359** : 1841-1850, 2002
20. Smith GW, Robinson RA : The treatment of certain cervical-spine disorders by anterior removal of the intervertebral disc and interbody fusion. **J Bone Joint Surg Am 40-A** : 607-624, 1958
21. Wu WJ, Jiang LS, Liang Y, Dai LY : Cage subsidence does not, but cervical lordosis improvement does affect the long-term results of anterior cervical fusion with stand-alone cage for degenerative cervical disc disease : a retrospective study. **Eur Spine J 21** : 1374-1382, 2012
22. Yamagata T, Takami T, Uda T, Ikeda H, Nagata T, Shinichi S, et al. : Outcomes of contemporary use of rectangular titanium stand-alone cages in anterior cervical discectomy and fusion : Cage subsidence and cervical alignment. **J Clin Neurosci 19** : 1673-1678, 2012