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ARTICLE

Effect of early treatment with zoledronic acid on prevention of bone loss in patients with acute spinal cord injury: a randomized controlled trial

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Abstract

Study design Randomized controlled trial.

Objectives To determine the effect of zoledronic acid on bone loss in people with acute spinal cord injury (SCI)

Settings Sawai Man Singh Medical College, India.

Methods Sixty patients with acute SCI were randomized to receive either standard treatment alone or standard treatment with zoledronic acid within 3 months after injury. Areal bone mineral density (aBMD) was measured at the hip using dual-energy X-ray absorptiometry (DXA) at baseline 3, 6, and 12 months.

Results Significant differences in aBMD were found between the standard treatment alone and standard treatment plus zoledronic acid group at the femoral neck (−0.13; 95% CI, −0.18 to −0.09, $p < 0.0001$), and total hip (−0.16; 95% CI, −0.19 to −0.12, $p < 0.0001$), respectively, at 1 year and bone loss was reduced in the zoledronic acid treated group as compared to the standard treatment group. Significant differences in aBMD between the groups at 6 months post infusion was also observed at these sites. [Femoral neck −0.08; 95% CI, −0.12 to −0.03; $p = 0.002$ and total hip −0.12; 95% CI, −0.15 to −0.08; $p < 0.0001$]

Conclusion A zoledronic acid 5 mg infusion given within 3 month significantly reduces bone loss at the hip after 6 months post infusion in patients with acute SCI.

Introduction

Osteoporosis following spinal cord injury (SCI) is well known and is indicated by low bone mass with deterioration of skeletal micro-architecture [1]. Disuse is considered the underlying cause of osteoporosis subsequent to acute SCI [2]. Unloading, neural lesion and hormonal changes after SCI result in severe bone loss [3]. Following SCI and immobilization, bone loss occurs rapidly in the pelvis and lower extremities in patients with SCI due to a marked increase in osteoclastic bone resorption and a decrease in osteoblastic bone formation [4]. The loss of mechanical stimuli in the form of muscle contraction and the lack of weight bearing due to SCI commonly results in sub-lesional osteoporosis [5, 6]. This consequently leads to increased fragility fracture risk commonly at the proximal tibia and distal femur [7–9] and resulting in fractures after trivial trauma or even spontaneously [10, 11]. Increased bone loss following SCI is associated with fragility fractures, morbidity and mortality, and substantial cost to the health care systems [1].

Bone loss is inhibited by bisphosphonates because they reduce bone resorption [4, 12]. Patients with acute SCI are treated in supine position for initial care and it is advised that oral bisphosphonates should not be taken by persons who are not able to stand or sit upright for at least 30 min. This is not possible in the initial SCI situation. Intravenous bisphosphonates therefore have an advantage over oral compounds like Alendronate [12]. Zoledronic acid is a 3rd generation bisphosphonate with more potent suppression of osteoclast mediated bone resorption than other congeners and can be given by once yearly intravenous infusion [13–15]. Therefore the purpose of this study was to evaluate the effect of early

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administration of zoledronic acid infusion on reduction of bone loss in patients with acute SCI.

Methods

Patients with SCI and neurological deficits (ASIA Impairment Scale A, B, C) were invited to take part in this prospective randomized interventional study if they sustained their injury within 3 months, were aged over 18 years, and were admitted to the department of physical medicine and rehabilitation between February 2013 and January 2015. Institute ethics committee approval was taken from Sawai Man Singh Medical College and Hospitals ethics committee, Jaipur, Rajasthan, India.

Patients were excluded if they had hypocalcaemia (serum calcium < 8.5 mg/dl), vitamin-D deficiency (serum 25(OH) vitamin-D < 25 nmol/L), significant renal impairment (creatinine clearance < 30 ml/min) or any history of adverse reaction to bisphosphonates, iritis, uveitis, psychiatric illness. Female participants who were pregnant, lactating, or planning to conceive were also excluded.

Sample size was calculated at 80% study power and alpha error of 0.05 assuming a standard deviation of 9% in aBMD in 12 months for a minimum detectable change of percent change in aBMD score of 9. Thirty patients in each group were included in the study. Informed written consent was taken to participate in the study. A blocked randomization schedule was generated by computer. Participants randomized to the control group received standard nursing and medical treatment. Participants randomized to the intervention group received the same standard nursing and medical treatment but also received an intravenous zoledronic acid (5 mg/100 ml) infusion. Neither participants nor investigators were blinded to group allocation but the assessor was blinded. The allocation sequence was concealed from the investigators responsible for screening and consenting participants.

aBMD was measured at the hip (femoral neck and total hip) at baseline once patients were medically stable and at 3, 6, and 12 months from date of injury by Hologic QDR-Delphi dual X-ray absorptiometry (DXA) machine in the Department of Radio-diagnosis, Sawai Man Singh Hospital, Jaipur.

aBMD variables obtained by DXA scans were normally distributed. But, mean derived from within the group differences and between group differences were not normally distributed. Boot strapping techniques were used to overcome this problem. Statistical analysis was performed on SPSS software version 16.0. The data were presented as mean ± standard deviation. Continuous variables were compared by paired *t*-test. Paired *t*-tests were used for actual/observed aBMD values within group and Independent *t*-test was used for absolute change for intergroup analysis. *P*-values <0.05 were deemed significant.

Results

A total of 212 patients with SCI admitted between February 2013 and January 2015 were screened for eligibility. A total of 152 were excluded because they did not meet inclusion criteria or declined to participate. Sixty eligible participants were assigned either to control group or to intervention group according to blocked randomization schedule (Fig. 1). Both the groups were comparable at baseline (Table 1). As a standard treatment, all acute SCI patients were treated with intravenous methylprednisolone acetate for 72 h and IM enoxaparin for 6 weeks following injury.

No significant differences in aBMD between groups were observed at 3 months at any of the sites of the hip. Similarly there was no significant differences at the femoral neck at 6 months (0.787 ± 0.095 vs. 0.806 ± 0.106, $p = 0.473$). But there was a significant difference at the total hip (0.785 ± 0.085 vs. 0.859 ± 0.129, $p = 0.014$) (Fig. 2).

Significant differences in aBMD were observed between the groups at 12 months at the femoral neck (0.729 ± 0.085 vs. 0.806 ± 0.102, $p = 0.003$) and total hip (0.734 ± 0.074 vs. 0.845 ± 0.125, $p < 0.001$) (Fig. 2).

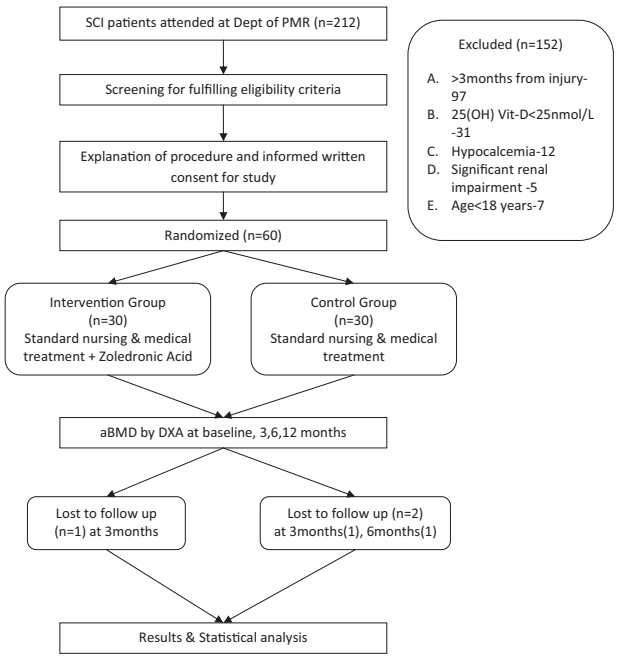

Fig. 1 Consort flow chart 212 SCI patients were admitted to the department of physical medicine and rehabilitation. All were screened for inclusion. Sixty patients were eligible for enrollment. They were assigned to either control group or intervention group based on the predefined computer generated random numbers. Baseline DXA scans were done once the patients were medically stabilized. Standard medical and nursing treatments were given to both the groups along with zoledronic acid infusion to the intervention group. Then follow-up scans were done at 3, 6, and 12 months. Two participants in the control group and one participant in the intervention group were lost in follow-up

Table 1 Baseline characteristics

Characteristics	Control group ($n = 28$)	Intervention group ($n = 29$)
Age (years)	35.57 ± 13.12	35.41 ± 13.45
Sex (male:female)	25:3	24:5
Height (cm)	163.3 ± 8.2	162.7 ± 7.2
Weight (kg)	53.1 ± 10.2	56.6 ± 9.6
Rural:urban	22:6	21:8
Alcohol intake	8/28	4/29
Smoker	9/28	3/29
Level of lesion (cervical/dorsolumbar)	C-20/DL-8	C-18/DL-11
Complete(AIS-A)/incomplete(AIS-B,C)	20/8	22/7
Corticosteroids given	22/28	20/29
Days to first DXA scan post injury	27.6 ± 10.6	27.5 ± 12.2
Days to zoledronic acid infusion post injury	NA	27.5 ± 12.2
Baseline areal bone mineral density (g/cm^2)		
Femoral neck	0.93 ± 0.13	0.87 ± 0.12
Total Hip	0.95 ± 0.10	0.90 ± 0.15

AIS–ASIA impairment scale

Values are mean ± SD unless stated otherwise

Alcohol Intake ≥180 ml/day, 3 times/week

Both the groups were comparable at baseline for demographic and anthropometric characteristics as well as factors associated with low bone mass and initial aBMD

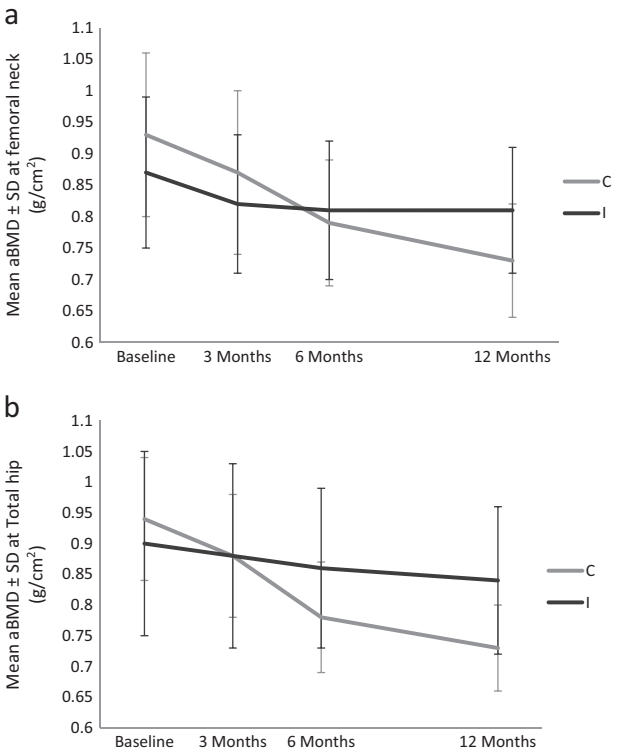

Fig. 2 Mean aBMD ± SD. Figure 2 shows mean aBMD (g/cm^2) ± Standard deviation of each group at baseline and 1st, 2nd, and 3rd follow-up at femoral neck **a** and total hip **b**

On intergroup analysis for absolute change in aBMD, significant differences were observed from 3 to 12 months. But there was non-significant difference at the femoral neck at 3 months (−0.01; 95% CI, −0.05–0.03; $p = 0.65$) (Table 2).

Zoledronic acid infusion was tolerated well and no adverse effects were documented. No participants had documented symptomatic hypocalcemia or renal function deterioration.

Discussion

Our study reaffirms that aBMD at hip decreases early and rapidly following acute SCI. Considerable reduction of aBMD at the femoral neck (19.7%) and total hip (21.1%) over 12 months was observed (Fig. 3; Supplementary file).

Similar to our study, Gilchrist et al. [16] also reported a randomized controlled trial on oral aledronate (70 mg/week) in 31 patients after acute SCI to demonstrate preservation of aBMD at all hip sites. The aBMD decline in their control group was similar to ours (total hip—20.9 ± 1.9%, trochanter—26.3 ± 2.4%, femoral neck—16.4 ± 2%). The treatment effect of aledronate on aBMD in this study was similar to the effect of zoledronic acid in our study.

Shapiro et al. [4] performed a double-blind, randomized, placebo-controlled trial in 17 patients with SCI which received zoledronic acid 4 or 5 mg once or placebo. They concluded that a single administration of zoledronic acid will ameliorate bone loss and maintain parameters of bone strength at the three proximal femur sites for 6 months and at the femur intertrochanteric and shaft sites for 12 months. However, Bubbear et al. [12] reported a randomized, open-label study of 14 patients with acute SCI randomized to receive 4 mg IV zoledronic acid or standard treatment. The reduction of aBMD loss was significant for total hip and trochanter but not for the femoral neck, probably due to the small patient numbers. Other studies also found reduced bone loss with oral alendronate and intravenous pamidronate [17, 18].Similarly Schnitzer et al. found zoledronic acid 5 mg infusion to effectively slow down the bone loss in the lower extremity (i.e., hip more than knee) compared to placebo [19].

Zoledronic acid given once within 3 months after SCI reduced bone loss at the hip and was well tolerated. IV zoledronic acid avoids potential adherence problems seen with oral bisphosphonates [20].

Table 2 Comparison of mean differences in aBMD at the hip between baseline and 3, 6, and 12 months follow-up among groups

Site	Control group ($N = 28$)		Intervention group ($N = 29$)		Mean (between group difference)	95% CI of difference		P-value
	Change score		Change score					
	Mean	Std. deviation	Mean	Std. deviation		Lower	Upper	
Comparison of mean differences in aBMD at Hip between baseline and 3 months follow-up among groups								
Femoral Neck	−0.05	0.06	−0.05	0.08	−0.01	−0.05	0.03	0.65
Total hip	−0.07	0.04	−0.02	0.03	−0.05	−0.07	−0.03	<0.0001
Comparison of mean differences in aBMD at Hip between baseline and 6 months follow-up among groups								
Femoral Neck	−0.14	0.09	−0.06	0.09	−0.08	−0.12	−0.03	0.002
Total hip	−0.16	0.06	−0.04	0.07	−0.12	−0.15	−0.08	<0.0001
Comparison of mean differences in aBMD at Hip between baseline and 12 months follow-up among groups								
Femoral Neck	−0.20	0.08	−0.06	0.09	−0.13	−0.18	−0.09	<0.0001
Total hip	−0.21	0.06	−0.06	0.05	−0.16	−0.19	−0.12	<0.0001

Mean and SD of the paired difference of absolute change of the aBMD at follow-up from baseline of both control and intervention groups at the femoral neck, trochanter, inter-trochanter, and total hip. Paired t-tests were used to compare baseline value with follow-up within group and unpaired t-test was used to compare change in values from baseline between control and intervention groups. Significant preservation of aBMD in the intervention group compared to the control group was observed in all groups except femoral neck at 3 months indicating significant prevention of bone loss

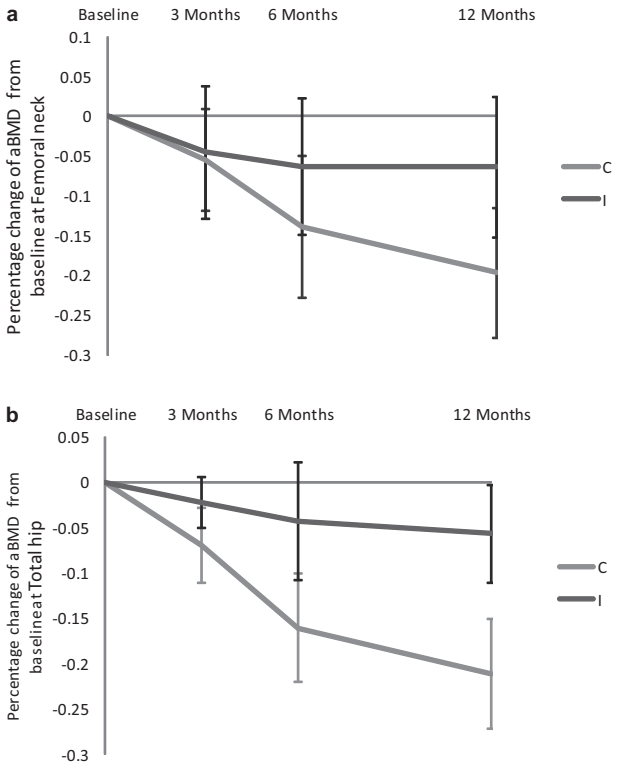

Fig. 3 Mean percentages change in aBMD from baseline (Supplementary file). Figure 3 shows the percentage change in aBMD from baseline. Derived from data obtained from follow-up scans and is documented as a proportion of baseline aBMD value lost subsequently during the study period

Limitations

Participants who regained ability to walk with aids were not considered separately, and the possible anti-resorptive effects of rehabilitation program (time of commencement and intensity) on preservation of aBMD were not considered.

Conclusion

Early treatment with zoledronic acid is an effective treatment for the reduction of bone loss at the hip for 12 months following SCI. But bone resorption continues due to off-loading of bone and further treatment may be needed. Also larger studies with a longer follow-up to assess the magnitude of bone preservation and further treatment with zoledronic acid are required.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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