Original Article

Safety and Tolerability of Intravenous Bisphosphonate Infusion to Improve Bone Mineral Density in Children with Spinal Muscular Atrophy at a Tertiary Care Hospital in India: An Observational Retrospective Study

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ABSTRACT

Background: Children with spinal muscular atrophy (SMA) have significantly reduced bone mineral density (BMD) compared to other neuromuscular disorders, predisposing them to frequent fractures. Despite this, bone health is frequently under-researched and under-managed in SMA care. Intravenous (IV) bisphosphonates, particularly zoledronate, reportedly improve BMD and reduce fracture risk in other disorders, with a favorable safety profile. This study aimed to evaluate the safety and tolerability of IV zoledronate in SMA type 2 pediatric patients in a tertiary care hospital. **Materials and Methods:** An observational retrospective study was conducted between June 2022 and July 2024. Twenty-two patients with SMA type 2 had their case notes from the SMA clinic retrospectively reviewed; of these, 8 patients (aged 5-17 years) with SMA type 2 had low BMD (Z <-2.5 on DEXA scan) who met the fitted inclusion criteria and received 0.05 mg/kg body weight of IV zoledronate every 6 months. Patients were monitored for adverse events (AEs), fractures, and clinical outcomes. **Results**: Fifteen infusions were administered in total; no serious Adverse Events (AEs) or adverse drug reactions (ADR) were observed. Grade I fever in 50% (3/6) of the females and infusion-related grade II pain in 87.5% (7/8) of the patients were observed, which resolved within 24 h with paracetamol. No patient required re-admission. Laboratory parameters and motor scales remained stable and no fractures occurred during the study period. **Conclusion**: IV zoledronate is safe and well-tolerated in children with SMA type 2 in their multidisciplinary management.

Key words: Spinal muscular atrophy, Zoledronic acid, Bone density, Drug Safety

Spinal Muscular Atrophy (SMA) is a group of rare neuromuscular disorders caused by biallelic loss or mutation (in 95% - 96% of cases) in the Survival Motor Neuron 1(SMN1) gene on chromosome 5q13, subsequently resulting in SMN protein deficiency [1, 2]. The α-motor neurons degenerate and neuromuscular junctions are disrupted, leading to progressive muscle atrophy and weakness of limb, trunk, bulbar, and respiratory muscles [3, 4]. The incidence of SMA is approximately 1 in 6,000-17,000 live births [1, 5, 6]. It has been the most common cause of genetic mortality in children before the introduction of advanced disease-modifying therapies (DMTs) [6, 7].

SMA is of four types based on symptoms, severity, age of onset, and highest motor milestone achieved [7,8]. The emphasis is now on early diagnosis and treatment for better response and prognosis, necessitating the implementation of newborn screening (NBS) worldwide [1, 9].

Poor bone health is the major comorbidity associated with SMA, which is attributed to the non-ambulatory status and diminished mechanical load on developing bone, resulting in disuse osteoporosis and fragility fractures [10, 11, 12]. This is due to the plausible mutation of SMN, with abundant osteoclasts interacting with signaling molecules like osteoclast-stimulating factor 1 (OSTF1) [13]. The bone remodeling and homeostasis are disrupted in SMA, by downregulation of osteoprotegerin (OPG) with increased activity of osteoclasts [14].

Despite this finding, studies of bone mineral density (BMD) are scarce in children with SMA, with some reporting it as normal and reducible with increasing age, while some say

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it is consistently low [10, 15]. To support bone health in SMA children, optimum calcium and vitamin D intake, along with physiotherapy and assistive devices, are essential [2]. There are no unanimous guidelines so far in the management of bone health for SMA patients, as outcomes vary depending on severity, phenotype, and DMT.

Intravenous (IV) bisphosphonate has been approved as an adjunct therapy under compassionate care guidelines for SMA [12]. This is important for countries where DMTs are not accessible. Zoledronate is an FDA-approved bisphosphonate that inhibits farnesyl pyrophosphate synthase, leading to suppression of bone resorption by osteoclasts [16]. There is a lacuna in the studies that used bisphosphonates, focusing on their safety and efficacy in children with SMA [2, 12, 13]. This study was done to evaluate the safety and tolerability of the bisphosphonate drug, Zoledronate, in SMA type 2 pediatric patients.

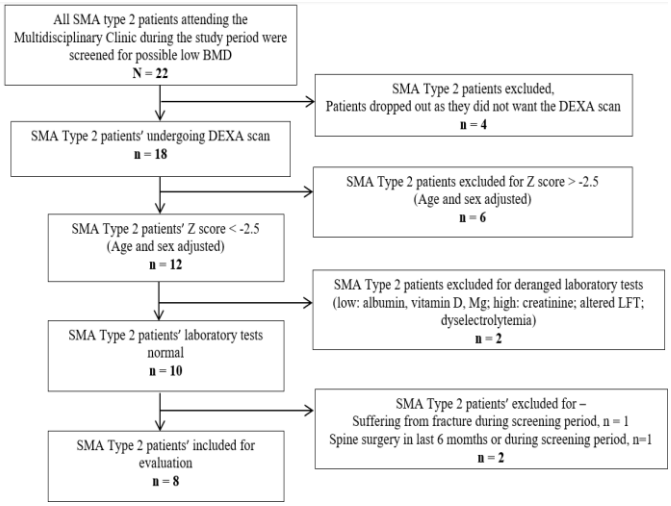
MATERIALS AND METHODS

Study Design and Patients

This was a retrospective study conducted at Peerless Hospital and BK Roy Research Centre, Kolkata, West Bengal, India, between the period of June 2022 to July 2024, wherein SMA type 2 patients were screened from the medical records. The included subjects were pediatric patients of >5 years & <18 years diagnosed with SMA type 2, who were sitters and not walkers, and who reported low Z-scores (<- 2.5), on a dual energy X-ray absorptiometry (DEXA) scan. SMA type 1 and type 3 patients, those who underwent recent spinal surgery, or presented co-morbidities like permanent ventilator support, or ongoing fracture treatment, and whose overall health was not suitable, were excluded from the study [Figure 1].

The ethical clearance was obtained from the Institute's Scientific and Ethics Committee and the medical records section for accessing patient data. Informed consent was provided by the participants, and patient confidentiality was maintained throughout the study.

The nutritional status of the patients was assessed, and those with a body weight more than the 3rd centile, with normal vitamin D, calcium, ALP-Alkaline Phosphatase, Albumin, and Globulin were only included in the study. The Hammersmith Functional Motor Scale Expanded (HFMSE) score was used for the baseline characterization of all patients biannually in the SMA clinic of the hospital as a part of a multidisciplinary care guideline for SMA patients [17]. HFMSE was used as a supportive clinical monitoring tool. Baseline blood tests for CBC, serum electrolytes, kidney and liver function tests, serum vitamin D and serum calcium and phosphate levels, and serum TSH, PTH levels were performed as a prerequisite for zoledronate Infusion therapy. Only patients whose blood tests were normal were included in the study [Figure. 1].



* N; total SMA type 2 patient pool, n; number of patients

Figure 1. Flow chart showing patient disposition.

Zoledronate Infusion

Patients were administered Zoledronate as per the protocol [2]. The patients were admitted on a day-care basis, and procedural consent was taken after explaining the procedure. Intravenous fluids (IV) were started to maintain adequate hydration. IV Zoledronic acid was administered at 0.05mg/kg body weight, infused over 2 h in 100 ml normal saline under standardized monitoring conditions, including continuous vital sign monitoring, pain assessment, and availability of emergency support for all the patients. IV paracetamol (15 mg/kg body weight) was administered if fever was reported. On discharge, paracetamol (15 mg/kg body weight) was advised to patients for fever, pain, or muscle cramps, if required. The caregivers or parents were requested to immediately report if there were any AEs. The infusion was repeated every 6 months.

Safety Assessments

AEs associated with zoledronate infusion were identified through retrospective chart review of inpatient infusion records, nursing notes, and infusion monitoring sheets, follow-up outpatient records, and laboratory investigations during scheduled follow-up visits. The AEs, serious AEs, and adverse drug reactions (ADRs) were reported using the Common Terminology Criteria for AEs (CTAE) guidelines. A grading severity scale has been provided for each AE. CTAE incorporates elements of the MedDRA terminology (CTAE v6.0). Careful monitoring of any immediate, early AEs, serious AEs, and ADRs post-infusion was performed. Incidence of fractures post-infusion during the follow-up period was also analyzed in the medical records of the patients. A follow-up was conducted for each patient every 3 months to assess the incidence of any fractures. Vitamin D levels, calcium, alkaline Phosphatase (ALP) monitoring, and HFMSE were repeated every 6 months.

Quality Control

All the data were double checked by the investigators, and before collection, the data were stored on a single strikeout policy.

RESULTS

Patient characteristics: Of the 22 SMA type 2 patients screened, only 8 (~36.4%) were eligible for the Zoledronate infusion therapy (Figure 1). The male-to-female ratio was 3:1, with an age range of 5 to 17 years, and a median age of 12 years. Five patients (62.5%) were given DMTs, of which three (60%) received Spinraza, and two (40%) received Risdiplam. The remaining (37.5%) patients were DMT-naive. The entire population received a total of 15 infusions, with a median of 2 infusions during the study period. One patient had a fracture 13 months before the infusion and hence was eligible for study (Table 1).

Table 1. Baseline demographics and patient characteristics

Safety

Patient Number	Sex	Age (Years)	DMT	Infusions received	Fracture history before screening
1	Female	5.11	Spinraza	1	1 fracture
2	Female	12	Spinraza	2	-
3	Female	13	Risdiplam	3	-
4	Female	12.5	-	2	-
5	Male	15	Risdiplam	2	-
6	Male	10	-	2	-
7	Female	17	-	2	-
8	Female	5.8	Spinraza	1	-

Safety: None of the study subjects reported fractures or any immediate, early, or late ADRs post Zoledronate infusion. 50% of the female patients reported Grade 1 fever, which lasted for a median duration of 24h. 87.5% reported Grade 2 pain, which subsided within a median duration of 24 h. No vomiting or other SAEs or AEs were reported. The findings are given in Table 2.

Table 2. AEs in the study population post zoledronate infusion

AEs	Patients (%)	Median Grade Score	Median Duration (h)
Fever	37.5	I	24
Pain	87.5	II	24
ISR	-	-	-
GI Disorder	-	-	-
Allergic reaction	-	-	-
Anaphylaxis	-	-	-
Muscle spasm	-	-	-
Cardiac Dysrhythmia	-	-	-
Musculoskeletal Pain	-	-	-
Eye Disorders	-	-	-

DISCUSSION

This retrospective chart review was done to evaluate the safety and tolerability of Zoledronate infusion in pediatric patients with SMA type 2 disease who had fractures earlier with low Z scores (<- 2.5), and to identify an adjunct therapy to treat the fractures associated with SMA. Since the cohort was small (n=8), this study can serve as a pivotal pilot trial to assess the safety of the drug infusion in SMA type 2 patients. Type 2 SMA patients comprise only ~29% of the total SMA pool, which itself is a rare disease [18], making the assessable patients low when a single center was considered for a registry study.

The only reported adverse effects were fever and pain for around 24 hours, which are the most observed AE associated with bisphosphonate infusion **[2].** As per The Indian Society for Bone and Mineral Research (ISBMR), a DEXA scan is recommended every 1 to 2 years [19]; however, since the study was done only to assess the safety and tolerability, the scan and, thus, post-infusion BMD were not performed. As per the general guidelines for Zoledronate infusion and post-infusion, monitoring bone density with DEXA scans within the first 3 years of infusion is expensive and will not give any notable difference [20]. Thus, it is not mandatory to recommend for patients in low-middle-income countries like India, where the accessibility for DEXA scan is also limited [19, 21].

For low-to-moderate risk patients, after 3 to 5 years of Zoledronate infusion, many guidelines suggest a 'drug holiday' or stopping the treatment. High-risk patients need prolonged infusions for better outcomes [22]. Many Indian pediatric and adolescent populations have low BMD owing to poor nutrition, high prevalence of obesity, impacts from chronic diseases, and genetic disorders [23, 24, 25]. The healthcare access for SMA children is a challenge in India, where the SMA awareness is low, coupled with its already reported overall poor bone health in the normal pediatric population. Thus, assistive therapies to improve bone health can aid in improving the Quality of Life (QoL) of SMA patients.

The studies on the impact of DMTs on bone health status and BMD are very few, with mostly contrasting outcomes. In the present study, the patients who received DMT and the untreated ones, both had low Z scores. Since the SMN mutation is linked to the plausible poor bone health and increased fractures in SMA patients, DMTs cannot supplement the fully functional SMN protein. In two retrospective studies, the authors reported that bisphosphonates were infused even in patients receiving DMTs owing to low Z scores [12, 13]. According to Tung JY and colleagues, children with SMA on DMTs mostly reported low BMD and a history of fractures; however, only a few of the patients met the criteria for osteoporosis as per the International Society for Clinical Densitometry (ISCD) norms

[13, 15]. This phenotype of SMA patients with osteoporosis would therefore require more careful bone health assessment and assistive therapies inspite if receiving DMT. Thus, the global clinical picture of bone health in SMA patients is underreported and requires more structured guidelines with a multidisciplinary approach for their management.

A single study had reported on the use of bisphosphonates as an adjunct therapy, showing improvements in the BMD; but the findings were not statistically significant, and the sample size was small, similar to the present one [2]. Under-reporting of mild AEs in retrospective chart reviews is another limitation. Large randomized trials can help to evaluate Zoledronate infusion in the multidisciplinary care for SMA. This will help to establish its safety and tolerability in a larger patient pool and assess its effectiveness in different phenotypes of SMA patients.

CONCLUSION

The results of the present study show that IV zoledronate is safe and well-tolerated in type 2 SMA pediatric patients. To establish these findings, larger randomized controlled trials in SMA patients with diverse phenotypes with zoledronate infusions as an adjunct therapy, along with DMT can be recommended in the future.

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