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Osteogenesis Imperfecta: Functional Outcomes in Jordanian Children Under Intravenous Infusion therapy of Pamidronate (Aredia)

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ABSTRACT

Background: *Osteogensis imperfecta (IO) is a hereditary disorder characterized by bone fragility and progressive bone deformity; intravenous pamidronate had been used in the treatment of severe OI for almost 20 years, and founded to be useful in enhancing bone density and decreasing bone fracture incidence, but little studies were showed the functional outcomes after this infusion of these patients using validated measures.*

Aim: *This study was conducted to describe the functional outcomes of children with OI under pamidronate infusion therapy among Jordanian children.*

Method: *This is cross sectional study was conducted for 15 children above 3 years of their age in Queen Rania Hospitals for children / Jordan from February – July (2015), and they had been diagnosed with moderate or severe OI, the Pediatric Outcomes Data Collection Instrument (PODCI) was used in this study to evaluate the functions.*

Result: *There were four items measured according to the global score of pediatric outcome instrument, the upper extremities with physical function showed (mean 72.4, SD 23.61) transfer and basic mobility (mean 53.6, SD 31.09), sports with physical function (mean 49.6,SD 23.36), and pain / comfort scales (mean 37.3, SD 26.03).*

Conclusion and Implication: *Pamidronate was assisted for upper extremities, basic mobility, sports function and pain for OI children with total global score 53%,while basic mobility showed a significant correlation with this infusion ($P< 0.05$) correlation coefficient = (0.566). Further evaluation are needed to show the long term outcomes of this therapy according updated protocol measures. The quality of life of children with OI needs to be in concern for patients and their families to apply holistic and optimal health care.*

Keywords

Osteogensis imperfecta, Pamidronate infusion, Functional outcome scale.

Introduction

Osteogenesis Imperfecta (OI) is an inheritance disorder characterized by decrease bone density due to the mutation of the gene that is responsible of collagen precursor which plays an important role in bone ossifications. Despite that OI is rare to occur, this disorder carry out incidence rate approximately 1 in 10,000 to 20,000 people worldwide, and prevalence rate in United States 25,000 to 50,000 [1].

Marini and colleagues [2] showed that Osteogenesis imperfecta caused by autosomal dominant, recessive and X-linked genes mutations, among 85% of the individuals it were autosomal dominant or classic type of this disease as popularly known in the past decade. Different mutations encoding protein responsible in type I collagen synthesis, processing, secretion and modification or proteins responsible either in bone-formation or differentiation process [2].

Sillence categorization (1979) classified four distinct types of this disease; depend on the clinical manifestations and genetic characteristics of this disease. Type I include patients with mild

manifestation and normal height, whereas type II is died in the maternal period. Type III is the most severe form in children surviving the neonatal period. These patients have well definite features like short stature accompanied with growth plate, progressive limb and spine deformities related to multiple fractures that occur, a moderate to severe phenotype that is not related to these categories are classified as type IV.

While there are many types of OI, the pamidronate therapies, had changed the bone mineral density and decrease fracture rate obviously according many studies, and the intravenous pamidronate is still have a golden role for treating children with OI [3,4].

An overview of many studies showed the fracture rate had been decreased in many children with OI. In meta analysis study, pamidronate were proficient in decreasing the incidence of fractures among children (RR = 0.80; 95% CI: 0.66–0.97), also Pamidronate infusions were useful on spinal bone density in the adult [3].

Within the context, Pulungan et al. [5] revealed in a cross sectional study of 41 children significant correlation between duration of therapy and fracture occurrence post infusion (p= 0.04).

Further to the concern, Constantino and colleagues [6] published a systematic review of 26 studies among children with OI, the randomized controlled trials reviewing showed no important improvement in mobility with oral pamidronate usage, while the reviewed studies pointed out that oral and intravenous pamidronate improved function and mobility.

Based upon the extensive literature review on intravenous pamidronate therapy, there were clear evidence supporting the usage of this infusion therapy upon bone mineral density and decreasing fracture rate.

Furthermore, there were little published studies that investigated the functional outcome of this high risk group and according of the researcher's knowledge, in Jordan no studies showed the functional outcome of pamidronate infusion therapy among Jordanian children with OI.

Methodology

Study design

Quasi experimental design of 15 children with moderate or severe osteogenesis imperfecta (OI) were included in cross sectional study from February – July (2015) of children who had taken intravenous pamidronate cycles for more than 12 months in duration. Legal and ethical approval of Royal Medical Services /RMS institutional board were performed before conducting this study.

Children were attended the metabolic clinic in Queen Rania Hospitals for children in RMS /Jordan either for follow up or for pamidronate cycle infusion ,children and their caregiver were informed about this study in the clinic with assistance of nursing staff their. Researcher insuring confidentiality of children and their caregiver before asking the questions, also they were informed about the ability to release from study any time if they wanted to give up.

Pamidronate (aredia) protocol according to the clinic protocol

Pamidronate infusion was given according to oxford pediatric endocrinology protocol (2015); patient above three years of their age the infusion dose 1.5 mg /kg/day diluted in normal saline 0.9% for two days, the repetitive cycle were performed after 3months of previous cycle.

Study sample and sampling

Male or female children above three years of their age, they became to the metabolic clinic in Queen Rania Hospitals for children in the regular follow up and for routine intravenous pamidronate infusion time were included in this study accompanied with their caregiver. Children had at least four cycles of intravenous pamidronate over 12 month of initial dose and they had improvement of bone mineral density from their base line z score according to DEXA scan.

Exclusion criteria

Patient less than 3 years of age; the researcher need to measure physical outcome that couldn't be measure in any age group upon this skeletal defects, children who take doses less than 12 months or with mild types with normal height and function also were excluded.

Patients Male = M Female = F	Current age / years	Types Moderate (III) Severe (IV)	Pamdominate cycle Each doses equal cycle	Onset duration of the diseases	DEXA showed improvement for lumber – spinal z score	
					Base line	Current score
M	10	III	10 doses	Since 6 years	- 4.0	-2.5
M	3	IV	7 doses	Since Birth	-3.0	-1.0
M	3	IV	7 doses	Since Birth	- 2.5	1.0
M	4	III	12 doses	Since Birth	- 6.0	- 4
F	8	III	4 doses	Since 3 years	- 6	2.5
F	12	III	4 doses	Since 2 years	- 6	1.5
F	7	III	12 doses	Since Birth	-9.0	- 4.0
F	8	III	6 doses	Since Birth	-2.5	4
F	3	III	4 doses	Since1 years	-3	-3.5
M	3	IV	10 doses	Since 1 month	-3.0	-2.0
M	8	III	15 doses	Since 5 months	-7.0	-2.0

M	5	III	4 doses	Since 4 months	1	1.5
F	5	III	7 doses	Since 7 months	-2.5	1.5
M	6	III	5 doses	Since 5 years	-2.5	2
F	3	IV	7 doses	Since 2 years	-1.0	3

Table 1: Demographical characteristics, diagnosis, and treatment data for patients.

Data collection

The Pediatric Outcomes Data Collection Instrument (PODCI) was developed in 1994 as effective tool used for wide range of children with multiple musculoskeletal disorders [7]. PODCI can be a trustworthy measure physical functioning for OI children, and offers important information about patient health status [8].

Four scoring scales were used in this study and there were an essential components of the global score; upper extremity / physical function scale which measures difficulty coming across performing daily personal care, transfer / basic mobility scale which measures difficulty may be comes from doing routine motion and motor in daily activities, sports/physical functioning scale which measures difficulty or limitations comes upon participating more active or sports activities, and pain/comfort scale that measures the level of pain experienced during activities.

Before to conduct this study for children who accept to be in the study by caregiver, the researcher had cached complete diagnostic and medical information for each patient with assistance of nursing staff, then they were be alone in the clinic room to ask them the questions for each scale in the global score.

Data analysis

Statistical analysis of data was performed using SPSS version 19, descriptive analysis showed cumulative scores of four scales independently, they were explored in table number two. The PODCI four functional assessment cumulative scores (upper extremity functioning, transfers and basic mobility, sports and physical function, comfort/pain) were calculated before statically analyzed.

The r correlation coefficient (Pearson) was also used to correlate pamidronate cycles with functional outcomes of each scale.

Result

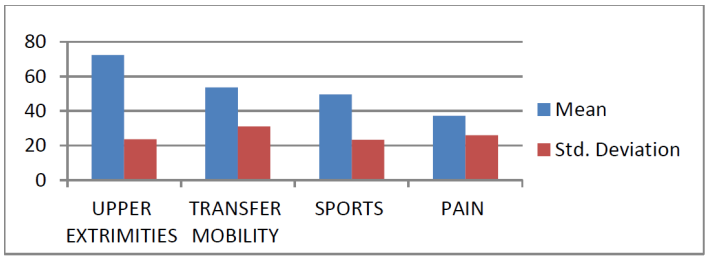
Participant Characteristics

The outline of the participant in this study showed (54%) male children and (46%) female children, with a mean age of 5 years, range 3.0-12.0 years. Underlying conditions included 73% of children with moderate types, and almost children had significant improvement in BMD as evident by DEXA scan Z score from their previous base line data. The mean average of pamdronite infusion cycles (7.73).

The results of the PODCI questionnaire are listed below in Table 2, and Figure 1. The higher the participants score, the higher their level of functioning in each scale. Children scored the lowest in the scale of pain (mean 37.3), while other scales; sports (mean 49.6), transfer mobility score (mean53.6), and upper extremities showed higher score (mean 72.4). Their overall Global Functioning score was with mean of 53.2.

Four scales	Mean	Std. Deviatio n	N
Upper Extremities	72.4453	23.61925	15
Transfer Mobility	53.6333	31.09532	15
Sports	49.6633	23.36044	15
Pain	37.3307	26.03887	15
Global score	53.222		

Table 2: Descriptive statistics of patients score for global scales.



The results of the PODCI showed a significant correlation between pamidronate (Aredia) and transfer basic mobility (P = 0.028) and correlation coefficient (0.566).

Discussion

The results of the PODCI showed that the mean of global score which includes the four scales, was above 50%, and that is clearly revealed pamdironate infusion was assist for functional outcomes for this high risk group, this is similar to the study was conducted by Marginean, Tamasanu, Mang, Mozos, and Brad [9] pointed out quality-of-life of the OI patients and their families was improved in many aspects like physical and mental health, especially the attendance of children schools.

Despite general improvement in functional outcome in these children, physical limitations still considered obstacles in two scales, and it had a significant impact on children daily life. They were unable to enjoy simple activities in transport and basic mobility like running, walking or sports participation and engaging outdoors peers activities; this was similar to Oliel et al. [10] when study pointed out physical quality of life QoL in children with OI be less than the general people, especially to severe OI types that reported bad QoL in these children.

Pain reduction was shown less than 50 % percent of accumulative score and lowest score among other scales, Garganta et al. [11] showed a study of pain assessment before and after completion of four weeks infusion cycles among these children; the study revealed pain increasing before consequent infusion and decreasing again after infusion, in this study the researcher didn't conduct a base line pain score before and after completion of infusion cycles.

In addition, the study showed an improvement of bone mineral density from base line data as recorded by DEXA scan z scores, and the care giver were be happy regarded the decrement of bone fracture incidence among their grown children, this was similar to many studies in the literature that confirmed a significant impact of pamidrnate infusion among children with OI bone density.

Furthermore, transfer and basic mobility were significant in correlation with pamdironate cycles, the pamidronate dose was given according to modified dose, and researcher need to correlate evidence between cycles number and cycles dose regard the functional outcomes within a safe manner, since the recommended dose had been given at a daily dose of 1 mg / kg over 4 hours or on 3 consecutive days repeated every 4 months; while modified protocol given at 2mg/kg over 4 hours or on 3 consecutive days and repeated every 4 months. Palomo et al. [12] pointed out that modified protocol showed a transient elevation in serum creatinine after infusion but normal serum creatinine after 12 months of completed cycles.

Conclusion and Clinical implication

This study represents the functional outcomes of pamidronate infusion using the PODCI in Jordanians OI children. The PODCI was effective instrument for this high risk group to measure their functional outcomes accurately. This study exhibits that significant increases in functional outcomes after pamidronate infusion in many domains; upper extremities, transfer/basic mobility, sports and pain for moderate and sever OI children, transfer and basic mobility were significant in correlation with pamdironate cycles.

Furthermore quality of life associated with physical functional improvement need to be in concern of this high risk age group and of their caregiver by applying holistic care approach.

In addition, researcher need to conduct other studies to show the recommended doses with different age groups that will improve functional outcomes according to updated protocol measurements in safe and appropriate manner.

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