Case Report

Clinical course in two children with Juvenile Paget’s disease during long-term treatment with intravenous bisphosphonates

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ABSTRACT

Juvenile Paget disease (JPD) is an ultra-rare disease, characterized by loss of function of osteoprotegerin. Osteoprotegerin inhibits osteoclast activation via the receptor activator of nuclear factor $\kappa B$ (RANK) pathway. Severely affected children suffer from bone deformities and pain and require long term anti-resorptive treatment. Due to the rarity of the disease, few long-term follow-up data on the clinical course in children are available.

In this report, motor development during infancy and early childhood and the activity of the bone disease based on clinical, radiographic and biochemical parameters are reported in 2 children with severe forms of JPD during long term treatment (4 and 14 years) with bisphosphonates. Results of a bone biopsy in patient 1 after 10 years of treatment and video material of the motor development of patient 2 are provided.

Doses per year of pamidronate ranged from 4 to 9 mg/kg bodyweight and were administered in 4–10 courses, yearly. Treatment was adjusted individually according to the presence of bone pain. Motor development was delayed in both children before treatment with bisphosphonates was commenced and improved thereafter. Bone histology revealed a significantly higher heterogeneity of mineralization which was mainly attributed to the increased percentage of low mineralized bone areas. Individualized intravenous treatment with pamidronate resulted in sufficient control of bone pain and suppression of bone turnover with few side effects over the observation period.

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1. Introduction

Juvenile Paget’s disease (JPD) (OMIM #239000; ORPHA: 2801) is an ultra-rare, heritable skeletal disorder, due to enhanced osteoclastogenesis and accelerated skeletal remodeling (Polyzos et al., 2018; Simont et al., 1997). Most JPD cases are caused by a loss-of-function of osteoprotegerin (OPG) (Whyte et al., 2003; Naot et al., 2005), caused by homozygous alterations in the TNFRSF11B gene on chromosome 8 (Polyzos et al., 2018; Naot et al., 2014; Grasemann et al., 2017). OPG is secreted by osteoblasts and serves as a soluble decoy receptor of the receptor activator of nuclear factor $k$B-ligand (RANKL), thereby limiting the osteoclast activation by the receptor activator of nuclear factor $\kappa B$ (RANK) pathway (Simonet et al., 1997; Cundy et al., 2005; Boyle et al., 2003).

Severe JPD is characterized by highly elevated bone turnover markers (BTMs) and fast skeletal remodeling, resulting in a painful, inflammatory-like bone disease (Cundy et al., 2011). Extraskeletal features include hearing impairment or deafness, retinal changes, extra-skeletal calcifications and Chiari Malformation (Polyzos et al., 2018; Grasemann et al., 2017; Kerr et al., 2010; Gottesman et al., 2016). Likely due to the rarity of the disease, few information on the motor and mental development in affected children is available. Reports have focused on the presence or absence of the ability to walk. In some children ambulation is achieved delayed (Saki et al., 2013; Chong et al.,...
2003; Cundy et al., 2002), some do not achieve ambulation or ambulation is lost as the disease progresses (Cundy et al., 2002; Cundy et al., 2004; Ralston and Taylor, 2019). Detailed assessments of motor development have not been reported to our knowledge so far. Mental development is reported to be impaired in a few cases (Grasemann et al., 2017; Cundy et al., 2002; Polyzos et al., 2014). However, impaired hearing is common (Polyzos et al., 2018; Naot et al., 2014; Gottesman et al., 2016; Cundy et al., 2004; Polyzos et al., 2014), and the development of deafness in young children is reported (Naot et al., 2014; Chong et al., 2003), which may further complicate the assessment of global development in childhood in this disease.

The pharmaceutical treatment of JPD focuses on suppression of bone turnover and mostly the administration of intravenous bisphosphonates is reported (Polyzos et al., 2018; Polyzos et al., 2009). Formerly calcitriol, synthetic osteoprotegerin and denosumab have also been used in this condition, but proved less effective or less safe than treatment with

![Fig. 1. Administered treatment (PMD = intravenous pamidronate; black triangles, the level represents the dose in mg per kg body weight (BW) per year and ranges from 5 to 9 mg per kg BW per year); (DNB = denosumab sc; green triangles) in patient 1 (A) and patient 2 (B). Course of total serum alkaline Phosphatase (TSAP in U/l) as a marker of disease activity, Trap5b (U/l) as osteoclast marker, osteocalcin (mg/ml) and renal deoxypyridinoline (DPD)/creatinine (ug/g); grey bars correspond to the age-appropriate reference range.](image-url)
biphosphonates (Cundy et al., 2005; Cundy et al., 2004; Polyzos et al., 2014; Grasemann et al., 2013; Doyle et al., 1974; Woodhouse et al., 1972).

Biphosphonates are analogues of pyrophosphate (PPi) and form a group of well-established drugs for the treatment of bone diseases associated with excessive bone resorption. Administration of biphosphonates results in an effective inhibition of osteoclast function with reduction of bone resorption (Recker et al., 2009; Baril et al., 2008; Boyce et al., 2014; Maksymowych, 2002).

In this report follow-up data on the clinical course of 2 children with a severe form of JPD are presented during long term treatment with intravenous pamidronate (PMD). The potential effect of the anti-resorptive treatment on the motor development is discussed and a video of the development of patient 2 is provided. In addition, histomorphometric analysis of the bone in patient 1 after 10 years of treatment is presented.

2. Patients, materials and methods

Baseline genetic, clinical and biochemical characteristics of both patients have been reported previously (Grasemann et al., 2017; Grasemann et al., 2013). Clinical and biochemical data were extracted from the patients charts. The photo and video material were provided by the parents of patient 2 and consent for publication was given. Long term BTMs and the dosage of the anti-resorptive treatments for both patients are displayed in Fig. 1A and B respectively.

2.1. Bone histology

The bone sample was immediately fixed in 70% ethanol, dehydrated in a graded series of ethanol and embedded undecalcified in polymethylmethacrylate. Three microns histologic sections for Goldner and Giemsa staining were prepared with a hard tissue microtome (Leica SM2500, Nussloch, Germany). Subsequently the surface of the residual sample block was prepared by grinding and polishing (Logitech PM5, Glasgow, Scotland) and carbon coated (Agar SEM Carbon Coater; Agar Scientific, Stansted, UK) for quantitative backscattered electron imaging (qBEI) evaluation as previously described (Roscher et al., 1998). The latter technique, including its calibration, is described in detail elsewhere (Roscher et al., 1998). Briefly, the qBEI images represent maps of calcium concentrations as the signal intensity of the electrons backscattered from the bone sample surface is dependent on the local calcium concentration. Frequency histograms of calcium concentrations (termed bone mineralization density distributions, BMDDs) can be deduced from the qBEI images as described previously (Roscher et al., 1998; Roscher et al., 2008) which provide information on the degree and heterogeneity of calcium concentrations.

2.2. Patient 1

Patient 1 is a now 16.6-year-old girl of Turkish descent with a severe form of JPD (TNFRSF11B:c.[2T. G]; [2T.G], who is being treated with IV biphosphonates for the last 14 years. Treatment was initiated at the age of 2.3 years and is being administered until present. Dosage and infusion intervals were tailored according to clinical needs and biochemical parameters (Fig. 1A). Currently, the girl has a near-final-height of 138.3 cm (with a growth velocity <1 cm/year over the last 1.5 years). Her calculated target height is 167.5 cm. Her older sister reached a final height of 168 cm. Detailed data on growth and growth velocity are provided in Supp. Tab. 1.

2.2.1. Motor development

Motor development in infancy was delayed. The patient learned to sit at age 18 months but displayed restricted movements of the lower extremities which seemed to be painful. At 26 months of age, she was able to pull herself up to standing.

At 31 months of age (2.3 years) treatment with intravenous (IV) pamidronic acid was initiated and her motor development improved. At 34 months of age, she was able to walk and remained ambulatory, except for episodes of bone pain, when she refused to walk. Due to a leg-length-discrepancy of 7 cm she has a limping gait.

2.2.2. Dosing of pamidronate

For a period of 5 years (2.3–7.3 years), she was treated with a total of 9 mg pamidronate/kg BW per year, administered in 3 cycles with 1 mg/kg/BW on 3 consecutive days. Bone pain, which resulted in refusal to walk, presented regularly 8–9 weeks after each cycle (parental report) and C-reactive protein (CRP) was frequently elevated (ranging from 0.00 mg/dl to 11.20 mg/dl [reference range: < 0.5 mg/dl] on multiple occasions) as a marker of inflammation.

Treatment intervals and dosing was changed at the age of 7.3 years to 0.75 mg/kg BW given every 4–5 weeks, again adding to a total dose of 9 mg/kg BW per year. The episodes of bone pain, which almost always localized to the lower extremities, were less frequent and less severe with this regime.

When Denosumab (Prolia®), a receptor activator of nuclear-factor-κ B ligand (RANKL) antibody, became available, the patient received two subcutaneous injections of denosumab at a 6-week interval. The clinical and biochemical response to this treatment have been reported previously (Grasemann et al., 2013). Due to severe side effects affecting calcium homeostasis this treatment was discontinued.

Anti-resorptive treatment was switched back to PMD. The yearly doses in the following years ranged from 5.6–9.2 mg/kg BW (Fig. 1A). PMD was given 6–8 weekly according to the clinical situation (bone pain). Delay of treatment promptly resulted in the development of bone pain and limping gait. Recently, treatment was switched to 0.025 mg/kg BW zoledronic acid to accommodate longer treatment intervals with less clinic visits during the pandemic.

Over the time, the patient suffered a fracture of her left tibia at the age of 7 years and patient 2 sustained three fractures: at the age of 1.6 she suffered fractures of the right femur when he fell of the changing table, and at age 4.7 years a fracture of the right tibia and fibula.

Her cognitive development is unremarkable, however no formal testing was undertaken. She is hearing impaired and required cochlear implants at the age of 8 years. Despite this, her speech development was unremarkable, and she communicates bi-lingual (Turkish/German) with little hearing-related difficulties. She attends a school for children with physical disabilities with good success. So far, there is no evidence of retinal involvement of the disease.

2.2.3. Bone sample

At the age of 12 years after 10 years of biphosphonate treatment, a bone sample of the femur was obtained during an osteotomy surgery in patient 1. Histology (Fig. 2A-E) revealed a bone sample with parallel trabecular-like features consisting of lamellar bone (revealing parallel bone lamellae under polarized light) together with woven bone (visualized by unorganized lamellae). The presence of bone formation showed a great heterogeneity. In addition to bone surfaces without formation (i.e. without osteoid seams), a large portion of the bone surface was covered by either thick osteoid seams devoid of osteoblasts or by thick osteid with multilayers of osteoblasts. Only very few osteoblasts are detectable, while in the bone marrow space several large (“giant”) osteoclasts with numerous nuclei could be observed. The BMDD based on qBEI imaging (Fig. 2F-H) showed a significant broadening of the BMDD peak (CaWidth Z-score +4.8), indicating increased heterogeneity in matrix mineralization. The percentage of bone areas with high (CaHigh Z-score +0.9) and those with low calcium concentrations (CaLow Z-score +3.0) were elevated. As a result of the latter, the mean mineral content (CaMean Z-score −1.1) was lowered. The most common mineral content (CaPeak Z-score −0.3) was within the normal range.
2.3. Patient 2

Patient 2 is a boy of German descent, who was treated with iv bisphosphonates for 4.5 years. The boy was born at 34 weeks of gestation (length 54 cm, weight 3.45 kg, head circumference 35 cm). A skeletal disease had been suspected antenatal because of widened and shortened femora (Grasemann et al., 2017). The patient presented with the clinical picture of an inflammatory disease, especially affecting the lower limbs. He was treated with ibuprofen and prednisone until a diagnosis of JPD (TNFRFS11B c.[25-28dup];[25-28dup]) was confirmed at age 13 months.

While movement in all extremities was limited in the newborn period (Supp. Video). Anti-inflammatory treatment resulted in some improvement, however, a distinct restriction of movements of the lower limbs is visible (Supp. Video: Minute 00:04). His motor development was assessed using the Munich Functional Development Diagnostics (MFDD)
At 13 months of age, his motor skills of the lower limbs were comparable to a child younger than three months, while motor skills of the upper extremities corresponded to a child of 12 months of age and was thus almost age appropriate. He was unable to sit or stand, and unable to lift his head in the abdominal position (Supp. Video, minute 00:25).

Treatment with intravenous pamidronate at 0.5 mg/kg/BW was initiated at 14 months of age. Consecutive doses were administered at 1 mg/kg/BW every 4 weeks and resulted in a swift improvement of his gross motor function. After 1 year of treatment, at 26 months of age, treatment intervals were extended to every sixed week. At this time, assessment of motor function via the MFDD revealed a sitting ability corresponding to a 9-month-old child. The motor development of the upper extremities with grasping was equivalent to a 16-month-old child. At the same time, he demonstrated independence and social behavior which was age appropriate (Supp. Video, minute 01:15).

At the age of 3 years, he was able to walk with little support. However, the patient developed bone pain and increased TSAP levels, necessitating shorter treatment intervals. Adjustment of the dose of pamidronate to 0.8 mg/kg/BW every 5 weeks caused side effects (vomiting). Treatment was tailored according to clinical and biochemical markers at 0.6 mg/kg/BW every 6 weeks and over time, motor development caught up to age-appropriate level. The patient was diagnosed with near-deafness at the age of 1.2 years. At age 2.5 he started to learn German sign language and communicated at an age-appropriate level with his caregivers. While his speech development was delayed/not present due to his deafness, his cognitive development was not impaired. Ophthalmological examinations were always unremarkable.

At the age of 5.6 years, the patient acquired a pneumococcal meningitis and deceased in a fulminant course. The patient reached a height of 106.4 cm (7th percentile). His calculated target height was 180 cm (50th percentile). For more growth data please refer to Supp. Tab 2.

3. Discussion

Both children of this report are affected by a severe form of JPD due to inherited homozygous mutations in TNFRSF11B (OMIM #239000) (Chong et al., 2003; Cundy et al., 2002). Severe forms of JPD1 are associated with a debilitating bone disease, short stature, Chiari Malformation and hearing and visual impairments (Whyte et al., 2002; Grasemann et al., 2017; Kerr et al., 2010; Whyte, 2006). Here, developmental aspects in two severely affected children are reported during long term treatment with bisphosphonates to extend knowledge on the course of the disease and to give information on the effects of long-term bisphosphonate therapy on bone turnover in children with JPD.

3.1. Motor development

Motor development was significantly delayed in both children in infancy. However, gross motor development progressed to almost age-appropriate norms during early childhood, after treatment with bisphosphonates was initiated. Delayed motor development has been reported in patients with JPD previously. (Whyte et al., 2002; Saki et al., 2013; Cundy et al., 2003; Cundy et al., 2002; Cundy et al., 2004; Ralston and Taylor, 2019). Saki et al. reported that bisphosphonate therapy lead to an improvement in motor skills (Saki et al., 2013).

Of note, the lower limbs seemed to be most affected in both children of this report, and this was present even before onset of weight bearing as shown in the video. Following weight bearing and walking, fractures and bowing deformities occurred in both children exclusively in the lower extremities. This distinguishes the disease from e.g. deforming forms of osteogenesis imperfecta, with resulting fractures and deformities of the entire skeleton (Marini et al., 2017). During early childhood, a refusal to walk likely resembled the onset of bone pain in the legs (Lücke et al., 2006). However, pain has not been assessed in a standardized manner in the patients of this report or in any other patient with JPD to our knowledge. It can be speculated that inflammatory bone disease is causative for bone pain with elevated levels of CRP in both children intermittently (usually at the end of the cycle of pamidronate therapy). Further, in patient 2 inflammatory-like periosteal bone lesions were seen at the end of a cycle of pamidronate therapy (Fig. 3A), that disappeared following intensified anti-resorptive treatment (Fig. 3B-D). Elevated inflammatory markers in JPD and a normalization after bisphosphonate treatment has been described in other reports as well (Grasemann et al., 2013; Wenkert et al., 2007).

It remains unclear to date why the lower limbs might be more affected by the disease. An effect of weight bearing is not likely the explanation, since the clinical presentation in infancy, as well as the video of patient 2 indicates that the lower limbs were more affected even before any weight bearing in form of standing or walking occurred.

3.2. Speech development

Delayed speech development in JPD has been reported previously (Naot et al., 2014; Gottesman et al., 2016; Saki et al., 2013) and it has been speculated that this occurs due to concomitant deafness (Naot et al., 2014). Speech development in patient 1 was normal, despite the fact that she was hearing impaired and required cochlear implants at the age of 8 years. In patient 2 speech development was not present/cannot be assessed, due to complete loss of hearing ability before the age of 1.2 years. However, he learned German sign language and communicated at an age-appropriate level with his caregivers. These findings support the hypothesis of the hearing impairment as the major cause for delayed speech development in patients with JPD.

3.3. Cognitive development

Cognitive development seemed unremarkable and age-appropriate in both patients of this report. However, no formal assessment of cognitive development was performed. Delayed mental development has been reported in patients with JPD before (Grasemann et al., 2017; Gottesman et al., 2016; Saki et al., 2013; Golob et al., 1996). In the report of 2016, a girl with JPD with and delayed cognitive development was reported. However, this patient had an underlying homozygous
deletion on Chromosome 8q24 which included TNFRSF11B and the COLEC10 gene causing 3MC syndrome [personal communication]. The developmental delay cannot be attributed to the phenotype of JPD in this case. Golob et al. reported on a 21-year-old patient with JPD and mental retardation (Golob et al., 1996). No information on the underlying genetic mutation is available for this patient.

In summary, it remains uncertain, whether impairment of cognitive development might be a feature in some cases of JPD.

3.4. Effects of pamidronate therapy

In rare bone diseases in childhood the question of duration, dosing and intervals of long term anti-resorptive therapies has been raised and discussed in the past, since recommendations for adult patients cannot be applied as guidance (Boyce et al., 2014). In high turnover metabolic bone disease, treatment aims to prevent deformities, bone pain and fractures (Polyzoz et al., 2018; Nait et al., 2014; Polyzos et al., 2009; Wenkert et al., 2007), but the benefits of intensive anti-resorptive treatment need to be weighed against the risk of side effects and over-treatment. Whyte et al. reported on a boy, who developed osteopenosis as the result of intensified bisphosphonate treatment with a cumulative dose of more than 2800 mg of pamidronate (Whyte et al., 2003).

Patient 1 was initially treated based on the originally published pamidronate schedule with 3-monthly infusions on three consecutive days and a 3-monthly pause (corresponding to 9 mg/kg BW/year), for the first 4 years. With this plan, a pause of 5 months between the last dose of cycle 1 and the first dose of cycle 2 occurs. There was significant bone pain resulting in refusal to walk during this pause. Therefore the schedule was changed to monthly administration of pamidronate in patient 1 and patient 2 was started with monthly courses (Tau et al., 2004). These administration intervals were tolerated well by both patients, the dosing was tailored to 4–6 mg/kg/BW/year. Side effects were present only in patient 2 with vomiting 2–4 days after the infusion and ceased when the dose was lowered.

In response to PMD there was a rapid improvement in pain and, as a result, in gait and motor function, lasting for a variable, but at least 4-week long, time interval following each administration. As described previously, fracture- and osteotomy healing was not disturbed in the children (Grassemann et al., 2017; Grassemann et al., 2013). This is in line with the evidence, that modern nitrogenous bisphosphonates such as PMD have no negative influence on fracture healing (Xue et al., 2014).

During therapy with PMD, there was an approximation of BTMs to age-appropriate norms (Fig. 1A and B). However, both, bone formation and resorption markers remained elevated. Due to the nature of the clinical visits, BTMs were assessed at the day of PMD treatment, thus resembling the ‘worst’ bone turnover at the end of each treatment cycle.

Treatment with PMD also resulted in a normalization of CRP and a decrease in inflammatory-like lesions on the lower extremity (redness, swelling, tenderness). Most impressively, PMD treatment resulted in a timely disappearance of the inflammatory-like periosteal lesions on radiograph in patient 2 after intensifying the treatment (Fig. 3).

In pediatric patients with high bone turnover disease there is increased risk of deformities during periods of rapid growth. While treatment with pamidronate was effective to control bone pain, deformities, especially in the lower limbs developed (Grassemann et al., 2017). One might expect that a less intensive anti-resorptive treatment would be sufficient, after cessation of growth, however Singer et al. reported data from a 20-year follow-up on three siblings with JPD and showed, that high bone turnover continues for many years in this disease, if left untreated. This resulted in osteopenia in this patient. Even at 32-years of age, start of bisphosphonate treatment resulted in a profound suppression of bone turnover markers (Singer et al., 1994). Severe osteopenia in an untreated JPD patient (for 20 years) has been reported by Whyte et al., as well (Whyte et al., 2002). Indeed, in patient 1 the treatment intervals could not be extended even when she reached near final height – due to bone pain arising 5–6 weeks after the pamidronate therapies. Switching to zoledronic acid allowed for longer treatment intervals (6-month). However, it is unclear whether this is an effect of the more potent drug, the pandemic situation with fear of hospital visits or the cessation of growth.

The femoral bone sample that was obtained after about 10 years of therapy with bisphosphonates showed highly parallel trabecular-like features (noteworthy resembling the observations by others (Salmon, 2004)). The sample revealed relatively high bone volume and thickness of the trabecular-like features, as well as the co-existence of secondary remodeled lamellar bone and woven/primary bone. It remains unclear whether the latter is a characteristic of JPD (Polyzoz et al., 2018; Whyte et al., 2002) or a typical feature for bone growth in this young patient. Noteworthy, woven/primary bone is commonly also found during growth in healthy children and is considered an efficient mechanism for mechanical stability during growth (Fratzl-Zelman et al., 2009). Except for this finding, histology also revealed abnormal multilayers of osteoblasts on bone forming sites, which to our knowledge have not been reported in JPD so far. Furthermore, and less surprisingly after long-term treatment with bisphosphonates, the number of osteoclasts attached to the bone surface was low. However, several larger osteoclasts with increased number of nuclei could be observed in the marrow space. Such “giant osteoclasts” have been reported to be a common finding after long-term bisphosphonate therapy (Jobke et al., 2014).

Further assessment of histomorphometric outcomes from this patient was not available as this is generally restricted to transiliac biopsy samples. However, as the bone matrix mineralization of trabecular bone is relatively constant throughout the skeleton of healthy individuals (Roschger et al., 2003), we were able to compare the femoral BMD outcomes with iliac crest reference data from children (Fratzl-Zelman et al., 2009). Our findings suggest a significantly higher heterogeneity of mineralization which can be mainly attributed to the increased percentage of low mineralized bone areas. These, in turn are indicative for still elevated high bone formation, since newly formed bone matrix has about 30% lower mineral content than old bone matrix due to the time course of secondary mineralization (Roschger et al., 2008). In view of the underlying disease, we hypothesize that without bisphosphonate therapy, the bone turnover might have been much higher in this child leading to much lower mineralization densities (shift of the BMD peak to the left). The bisphosphonate therapy decreased bone turnover (as seen also by the time course of bone markers) and shifted the mineralization densities toward normal values (thereby normalized the most frequent calcium concentration CaPeak). The increased amount of highly mineralized areas (CaHigh), however, is the result of the considerable presence of woven/primary bone which has a higher mineral content than secondary remodeled lamellar bone (Fratzl-Zelman et al., 2009).

4. Limitations

Limitations of the present work include the small number of patients as is the nature of case reports in ultra-rare diseases. Furthermore, the natural course of the disease is not understood, due to the rarity of the disease and the different severity of JPD based on differing underlying mutations. Case reports can only be generalized to a limited extent. However, it is these facts that make the reporting of individual cases necessary and there is a need for registries to collect data on ultra-rare diseases in order to improve our knowledge and offer patients optimal treatment.

5. Conclusion

Treatment with individually tailored doses and administration intervals of intravenous pamidronate in children with severe forms of JPD seems to be safe and effective. This likely applies to other bisphosphonates as well. Our very limited knowledge on the natural cause of JPD, effects in-utero, the newborn period, childhood development, treatment
options and pathophysiology in different organ systems of this ultra-rare disease is not tolerable in the 21st century with the possibilities of data sharing in the medical community. Registries on rare diseases, such as EuRECA (Ali et al., 2020) and EuRR-Bone must aim to connect individuals, care givers and doctors to ensure a rapid improvement of our knowledge.

Supplementary data to this article can be found online at doi.org/10.1210/jc.2019-2005.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CRediT authorship contribution statement

Study design: CG, JH; Study conduct: CG; Data collection: JH, KS, BMM; Data analysis: JH, CG, BMM; Data interpretation: JH, KS, CG; Drafting manuscript: JH, BMM, and CG; Revising manuscript content: BMM; Data analysis: JH, CG, BMM; Data interpretation: JH, KS, CG; Approving final version of manuscript: all.

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Study design: CG, JH; Study conduct: CG; Data collection: JH, KS, BMM; Data analysis: JH, CG, BMM; Data interpretation: JH, KS, CG; Drafting manuscript: JH, BMM, and CG; Revising manuscript content: KS, MMS, MH, TL; Approving final version of manuscript: all.

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