ISSN: 3032-3134 (ONLINE)
InaJBCS Indonesian Journal of Biomedicine and Clinical Sciences

The role of bisphosphonate and bone morphogenetic proteins in congenital pseudoarthrosis of the tibia management: a literature review

Panji Sananta[1]*, Adithya Stephana Mahendra[1], Eka Noviya Fuzianingsih[2]

[1]Department of Orthopaedic and Traumatology, Faculty of Medicine, Universitas Brawijaya/Saiful Anwar General Hospital, Malang, Indonesia, [2]Master of Immunology Study Program, Postgraduate School, Universitas Airlangga, Surabaya, Indonesia

https://doi.org/10.22146/inajbcs.v57i2.20291

Submitted: 2023-10-05
Accepted : 2024-10-03

ABSTRACT

Congenital pseudoarthrosis of the tibia (CPT) is a rare medical condition characterized by a congenital absence of union in the tibia, which causes the leg to flex anterolaterally. Despite the use of several surgical techniques for the treatment of CPT, there is still a significant risk of failure with surgical interventions. Recent studies have shown that bisphosphonates (BP) and bone morphogenetic proteins (BMP) can be effective adjuncts to surgical procedures, increasing the success rate of bone union and reducing the chance of re-fracture. This review aimed to evaluate the role of BP and BMP in CPT. In this review, a comprehensive literature evaluation was conducted using the PRISMA method. The databases used to search for information included PubMed, ScienceDirect, and Google Scholar for the past 10 years. Six articles were included in this review. The results showed that using pharmacological agents such as BMP and BP is considered safe for pediatric patients as an adjunctive treatment to surgery. This combination can effectively increase the speed of bone union and prevent re-fractures. The small sample size, different protocols, and different doses may have impacted the study results, which should be thoroughly explained.

ABSTRAK

Congenital pseudoarthrosis of the tibia (CPT) merupakan suatu kondisi medis yang jarang terjadi, ditandai dengan tidak adanya penyatuan bawaan pada tibia, yang menyebabkan kaki tertekuk ke arah anterolateral. Beberapa teknik bedah digunakan untuk pengobatan CPT, namun intervensi bedah tetap memiliki risiko kegagalan yang signifikan. Penelitian baru-baru ini menunjukkan bahwa bifosfonat (BP) dan *bone morphogenetic proteins* (BMP) berpotensi sebagai tambahan untuk prosedur bedah, sehingga meningkatkan tingkat keberhasilan penyatuan tulang dan mengurangi kemungkinan terjadinya patah tulang kembali. Tujuan dari tinjauan pustaka ini adalah untuk mengetahui aktivitas BP dan BMP pada CPT. Metode yang digunakan dalam tinjauan pustaka ini mencakup kajian pustaka yang komprehensif dengan menggunakan metode PRISMA. Basis data yang digunakan publikasi di PubMed, ScienceDirect, dan Google Scholar selama 10 tahun terakhir. Terdapat enam artikel yang dimasukkan dalam kajian. Hasil kajian menunjukkan jika penggunaan BMP bersama BP aman untuk pasien anak sebagai pengobatan tambahan dalam pembedahan. Kombinasi ini secara efektif dapat meningkatkan kecepatan penyatuan tulang dan mencegah terjadinya patah tulang kembali. Ukuran sampel yang kecil, protokol yang berbeda, dan dosis yang berbeda mungkin berdampak pada hasil penelitian, sehingga harus dijelaskan secara menyeluruh.

Keywords:
bisphosphonates;
bone morphogenetic proteins;
congenital pseudoarthrosis of tibia;
review;
effectiveness

*corresponding author: panjisananta@ub.ac.id

INTRODUCTION

Congenital pseudoarthrosis of the tibia (CPT) is a condition in which the tibia fracture does non-union after a history of trauma to the previously platinized bone.[1,2] This is associated with an increased tendency to fracture again. It is usually considered one of the most frequently observed types of congenital pseudarthrosis. It is widely regarded as one of the most common types of congenital pseudoarthrosis. The most common predisposing conditions for CPT are anterolateral bowing, tubular failure early in life, and cystic pre-fractures.[2]

Most CPT cases are discovered in the first two years of life.[1] Rarely, 1 in 150,000 babies has CPT which it is often associated with autosomal dominant neurofibromatosis-1 (NF-1), which affects 1 in 4,000 live births. Although 40-80% of CPT cases are NF-1 carriers, only 4% had CPT and tibial bending.[2,3] Before identifying this disease, infection, rickets, benign or malignant tumors, and faulty osteogenesis must be checked out.[1]

Orthopedics continues to face challenges in managing CPT due to difficulty achieving and maintaining functional limb union. This condition represents a distinct and complex type of pediatric fracture. Some CPT cases cause family unhappiness due to unsuccessful surgeries and shortened, misshapen, and malfunctioning limbs.[1,4,5]

Congenital pseudoarthrosis of the tibia surgery only aims to repair limb length disparities and restore limb alignment while maintaining articular function.[2] After that, therapeutic interventions like bone grafts with stable external fixation loops or intramedullary rods have been widely adopted and expanded, resulting in successful osseous union. In the last two decades, supplementary therapies like bisphosphonates (BP) and bone morphogenetic proteins (BMP) have gained favor due to good initial results and bone union.[7] Biphosphonates has long been used to limit bone absorption in osteoporosis and osteogenesis imperfecta patients by inhibiting osteoclast activity. Recent research suggests that BP as surgical and separate BMP adjuncts may improve bone union and reduce refracture.[8,9]

Since Marshall Urist created the term BMP in 1965 to describe a demineralized bone matrix component that might cause new ectopic bone growth, more than 20 BMPs have been discovered. Only rhBMP-2 and rhBMP-7 are clinically available. Many BMP studies have shown success in treating tibial pseudoarthrosis. Concerns about BMP safety in children, such as side effects, carcinogenesis, and growth plate effects, may limit studies. BMP-7 has been used to treat CPT with mixed results.[3] The BMP-2 increases mesenchymal cell proliferation and chondroblast formation, while BMP-7 promotes osteoblast differentiation.[10]

Children with systemic osteopenic diseases, including osteogenesis imperfecta (OI), have received BP without side effects for a long time. BP alone cannot increase the osteogenic capacity of hamartoma stem cells. The authors concluded that BP and other stimuli must be combined to increase bone growth.[11] Bisphosphonate alone did not boost the osteogenic potential of hamartoma stem cells. However, by reducing osteoclastic bone loss, BMP and BP may help preserve BMP-induced bone formation.[9]

According to the understanding of the problems that are associated with CPT, the primary goals of CPT therapy include the following: first, correcting the anterolateral bowing at the CPT location; second, achieving and maintaining tibial harmony at the CPT location; third, achieving fibular consolidation; and last, reducing or preventing proximal fibular migration. Correction of ankle, foot, hip, and leg length discrepancy (LLD) deformities are secondary treatment

goals.[2]

Given the significant impact that CPT has on child development, growth, quality of life, and costs and the high failure rate of the repair procedure which may result in lifelong disability, it is imperative to prioritize the development of a successful approach over the identification of specific factors.[12] As new pharmacologic agents are discovered and a better understanding of the pathophysiology and etiology of the disease is gained, surgical approaches will evolve to include more advanced technologies and treatments.[13] Research on BMP and BP is still limited, so a comprehensive review is needed regarding the use of these two treatments in patients with CPT.

MATERIAL AND METHODS

This study intends to conduct a textual analysis in English as part of the literature review. The documents were selected based on PRISMA principles. In July 2023, the research publications were analyzed using three databases: Science Direct, PubMed, and Google Scholar.

The journals were divided into three sections. The initial stage is to identify duplicate data across many data sources. The following stage was article selection, which included a review of abstracts and titles. The final stage was a thorough examination to see whether the article's primary focus was on the role of BP and BMP in CPT illness.

The inclusion criteria in journal selection were studies that discussed the role of BP and BMP in CPT disease, published in English within the last 10 years and were full-text articles. Abstract articles and case report publications were excluded from the journal selection. The keywords used in this search were "bisphosphonate", "bone morphogenetic proteins", and "congenital pseudoarthrosis".

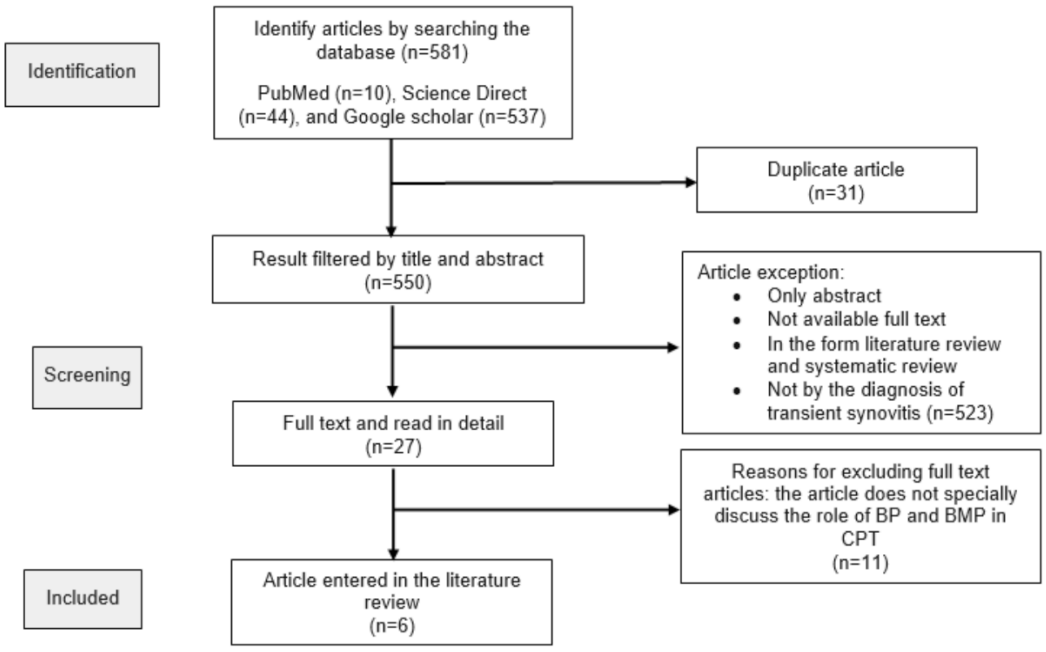

FIGURE 1. The flowchart of article selection

RESULTS

The search results found 581 journal publications, with 10 articles sourced from PubMed, 44 from Science Direct, and 537 from Google Scholar. The duplication filtering algorithm identified 31 articles with similar content. By examining the titles and abstracts, we found 550 journals using the filtering technique. Subsequently, 523 articles were excluded based on predefined exclusion criteria. This left 22 journals to be thoroughly examined, and it was found that 11 studies did not provide sufficient details on the involvement of BP and BMP in CPT disease. This is because there are journals that use additional active ingredients other than BP and BMP that the author knows about through the procedure section. The journals selected and used for review were journals that only discussed the use of BP and BMP as additives in surgical procedures. After completing the above 3 stages, we critically analyzed the content of the 6 articles obtained.

TABLE 1. Characteristic of article

References	Aim	Design	Procedure	Results
Bobyn *et al.*[14]	Evaluate the benefits of a surgical model in Nf1-deficient mice (Nf1+/-) with and without systemic BP treatment.	Randomized control trial and used 16 wild-type mice Nf1 gene heterozygous mutant.	**Surgery:** During surgery, 5 mg of rhBMP-2 was put on two paravertebral acellular collagen sponges (ACS) on each side of the animals to help them fuse. The lumbar spine was fused from L4 to L6 surgically. **Radiography :** Micro-CT measurements of the fusion mass's bone volume and mineral content. The fusion mass was kept in a uniform ROI by software. **Histology :** The specimens were stained with Picro Sirius Red and Alcian Blue to differentiate bone and cartilage.	After the BP operation, the animals were OK. At 3 wk, a sizeable osseous aggregation was touchable and occasionally visible atop the lumbar vertebrae. The total bone volume (BV) and density of Nf1+/- mice's fusion masses were 11% significantly lower than wild-type controls ($p = 0.08$; $b = 0.34$). This suggests that a larger sample size may deliver essential results.
Das *et al.*[15]	Evaluate how intramedullary K wire and autologous bone grafting help CPT patients heal fractures over 5 yr. It also looks at how well rh-BMP-7 and surgery work compared to a control group that only gets surgery.	This randomized experiment involved 120 CPT patients from 2002 to 2007. Patients were tested for NF1 and pseudoarthrosis. 20 patients divided into 2 Groups. Group 1 (2 boys and 8 girls, mean age 4.2 y.o., 4 left and 6 right tibia) and Group 2 (5 boys and 5 girls, mean age 4.1 y.o, 8 left and 2 right tibia).	Twenty patients were CPT Crawford type IV and 100 were NF1 and used the intramedullary K-wire procedure. 3.5µg of rhBMP-7 and an opposite-side donor tibial graft. Group 2 had the same surgery as Group 1, minus rhBMP.	Refracture occurred in 3 patients of Group 1. After lower leg damage, 1 patient developed refracture after 10 mo, and the other 2 after 6 and 7 months. During the 5 yr follow-up, 4 patients of Group 2 patients sustained fractures lasting 4 to 8 mo. At the final follow-up, 1 patient in each group failed to achieve union and was classified as Johnston grade 3. Two patients refused unionization.

TABLE 1. Continued

References	Aim	Design	Procedure	Results
El-Hoss *et al.*[16]	This study will determine if PD0325901 alone or with rhBMP-2 speeds up NF1 pseudarthrosis healing in mice.	Retrospective study used 55 $Nf1^{flox/flox}$ mice the National Cancer Institute mouse and an intramedullary rod procedure. $Nf1^{flox/flox}$ WT mice were killed on the fifth day to create calvarial cultures. By combining $Nf1^{flox/flox}$ mice with Z/EG reporter mice, transgenic mice were created. The animals utilized have to be WT or $Nf1^{flox/flox}$.	Fractures appeared in 11 wk old specimens. For rhBMP-2-containing open fracture research, closed fractures and periosteum were generated. With or without 10 mg rhBMP-2, the AdCre virus was put into a strip of collagen sponge for clinical use. Sponge and suturing covered the fracture. The experimental participants received 10 mg/kg/day of PD0325901, a MEK inhibitor, from day 22 before surgery to day 10 after surgery. A thorough evaluation includes histological analysis, radiography, and mechanical testing.	Western blotting showed that RhBMP-2 did not change the amount of phosphorylated ERK in WT cells treated with AdGFP. Treatment with PD0325901 did not influence cartilage or fibrous tissue buildup. Additionally, PD0325901 did not enhance fracture strength. Combining PD0325901 and rhBMP-2 resulted in an 80% union rate, much greater than the 69% found with rhBMP-2 alone ($p<0.05$). These findings suggest that MEK inhibition alone did not save the Nf12/2 fracture model. When used with rhBMP-2, it may boost bone development.
Papanna *et al.*[17]	Assess BMP-2's safety and efficacy in treating chronic non-unions in pediatric patients with severe medical problems.	This study examines Sheffield Children's Hospital rhBMP patients from October 2006 to November 2010 and is a cross-sectional study. The final sample included 15 patients.	The final sample included 15 patients who had 17 surgeries. The average age of rhBMP-2 recipients was 9.5 yr (4 - 15 yr). There were 6 men and 9 women. After sterilization, the BMP-2-infused sponge was soaked in 1.5 mg/mL sterile water for 15 min. Slices of sponge were placed immediately over the bone points. Clinical and radiological evaluations continued until the union.	The average union lasted 16 wk (10 to 28 wk). At the final follow-up, 16-17 sites showed clinical and radiological improvement. A single patient with Coats' plus disease and tibial non-union received BMP-2 and an Ilizarov fixator 10 mo after the initial procedure. The surgery was 10 mo before treatment. Treatment failed to promote recovery. No participants had BMP-2-related local or systemic problems. No patients under surveillance had wound disintegration, local soft tissue calcification, or heterotrophic ossification.

TABLE 1. Continued

References	Aim	Design	Procedure	Results
Deo *et al.*[18]	The purpose of the study was to assess the effects of administering rhBMP-2 and/or ZA on the individuals who participated.	Randomized control trial and used 60 $Nf1^{flox/flox}$ mice. The study tested four groups: vehicle controls, which received Ad-cre virus only; ZA only; rhBMP-2; and rhBMP-2/ZA.	Animal surgeons performed open tibial mid-shaft fractures on 10–12 wk old female $Nf1^{flox/flox}$ mice. An earlier approach was improved to induce a tibial knockout by local delivery of the pure recombinant Ad-Cre virus. This variant administered the virus onto an absorbable collagen sponge saturated with a rhBMP-2 implant kit. Digital X-rays assessed radiographic healing at 1, 2, and 3 wk post-surgery. After 3 wk of recovery, fractures were collected and scanned in saline without formalin fixation. We used an Instron 5944 (MA) mechanical testing equipment to perform four-point bending tests on contralateral tibiae and fractures that healed in 3 wk (rhBMP-2, n = 10; rhBMP-2/ZA, n = 11). Only populations with a statistically significant bone fusion rate were evaluated.	After 3 wk of therapy, bone union was much better than with vehicle and ZA alone ($p<0.01$). All fractures treated with ZA healed entirely or partially. ZA administration led to a moderate increase in BV (3x, $p<0.01$) without an increase in union rate. The rhBMP-2 administration led to a 12-fold increase in hard callus volume ($p<0.01$ vs. vehicle and ZA groups), with a more significant effect in the rhBMP2/ZA group ($p<0.01$ vs. all groups). After 3 wk, rhBMP-2-treated Nf1null fractures were weaker than the opposite-side tibiae. The co-treatment of rhBMP2/ZA resulted in greater strength than rhBMP-2 alone ($p < 0.01$) but did not differ from the contralateral leg. The 2 ZA-treated groups had the most minor fibrous tissue, <5%. BMP-2/ZA specimens reduced fibrous tissue by 76% compared to BMP-2 alone ($p = 0.068$).
Shannon *et al.*[19]	The initial Paley cross-union procedure results in only internal fixation.	A study used 36 patients. Medical imaging and record data were analyzed. from patients with a CPT diagnosis, Paley cross-union protocol therapy, and at least 24 mo of follow-up data. All radiographic CPT instances were classified Paley-wise.	After 12 wk, all cross-union surgery patients received another ZA. All patients received BMP2 off label. The surgeon followed the lead investigator's protocol. Patients had radiographs taken before, after, and at the latest follow-up.	All 39 CPTs had a complete tibia union and fibula cross-union after the index operation. All but two cases of fibula congenital pseudarthrosis/osteotomy healed. No patient's tibia or fibula broke again throughout the 24- to 85 mo follow-up.

DISCUSSION

The findings of this study were obtained from previously published articles. This study aimed to determine the role of BPs and BMPs in congenital pseudoarthrosis of the tibia. One of the articles selected for this literature review involved the use of a cross-sectional approach to determine the involvement of BP and BMPs in CPT.

Studies carried out by Bobyn *et al.*[14] Deo *et al.*[18] and Shannon *et al.*[19] employed zoledronic acid (ZA) and rhBMP-2 in the treatment of CPT. Bobyn *et al.*[14] reported that the concurrent administration of rhBMP-2 and ZA resulted in a significantly increase in the bone volume of the fusion mass ($p<0.01$) in both wild-types and $Nf1^{+/-}$ mice when compared to the administration of rhBMP-2 alone. When both treatments were given together, the general bone mineral density of the fusion mass went up in a significant way ($p<0.01$). The study also had similar results to Bobyn *et al.*[14] did showed that using both rhBMP-2 and ZA is better than just using rhBMP-2. People with NF1 pseudoarthrosis have been treated in the past with rhBMP and BP medication. However, it has also shown general effectiveness in different orthopaedic model.[20,21]

Deo *et al.*[18] reported that the co-administration of rhBMP-2 and ZA, a potent bisphosphonate, led to a significant increase in mechanical strength and restoration of the affected limb. Zoledronic acid has a strong preference for bone sites and only goes to places where the bone is changing. Based on the benefits seen in the $Nf1^{+/-}$ fracture model, it was expected that the above treatment, when combined with rhBMP-2, would work well in the Nf1-null model. The report of Deo *et al.*[18] showed that the combination of rhBMP-2 and ZA resulted in the highest bone volume and better mechanical strength. It has been seen that giving rhBMP-2/ZA to a Nf1-null fracture model, which is similar to NF1 pseudarthrosis, speeds up bone growth and makes it more likely that the bone will heal. In addition, it has been reported that the concurrent administration of ZA can reduce the occurrence of fibrosis in the area of the fracture, a complication that may be intensified by the use of rhBMP-2 treatment in isolation.[22]

Research conducted by Shannon *et al.*[19] revealed that using a combination of ZA and rhBMP-2 showed no fractures during a follow-up period of up to 7 years despite certain complications such as stem fussier-duval (FD). Nevertheless, the aforementioned did not have a detrimental effect on the crop output and was rectified during the scheduled stem replacement procedure. All patients in the external fixation cohort achieved complete tibial fusion and exhibited no refracture for a minimum of 24 mo, as evidenced by a 7 yr follow-up. The likelihood of a successful interactional union between the present set of external and internal cross-fixation fusion protocols is 100%.

The results of the analysis suggest that rhBMP-2 was successfully administered to patients with minimal negative effects. The aforementioned observation aligns with the results reported, by Papanna *et al.*[17] wherein the mean duration until the union was 16 wk, with a variation of 10 to 28 wk. In the study group, no adverse effects related to BMP-2 administration were observed. Clinical and radiographic healing occurred at 16 of the 17 hospital sites. According to the study results, BMP-2 has a positive effect on the healing of chronic non-unions without having any bad effects. The current study shows how rhBMP-2 can be used effectively as a part of a treatment plan for recurrent non-unions in pediatric patients who haven't gotten better with traditional therapies.

Administration of ZA and BMP-2 in 39 CPT patients achieved complete tibial union and comprehensive cross-union

between the tibia and fibula. Except for two participants, all individuals exhibited successful healing of their congenital pseudarthrosis or fibula osteotomies. Administration of ZA 2 wk before surgery ensures the effective incorporation of BP into the bone graft before its harvesting. The use of BMP2 may have the advantage of accelerating the osteogenic response.

Cross-union bridging was seen in the majority of cases as early as 6 wk after surgery. Carlier *et al.*[24] conducted an *in silico* clinical trial and reported that BMP intervention resulted in a reduction in the severity of CPT. However, it was observed that the outcomes were subject-specific. Birke *et al.*[9] performed surgery with IM fixation, bone transplantation in certain patients, and BP in conjunction with BMP-7, as well as a ZA infusion afterwards. According to their findings, 75% of primary unions are fracture-free.

Birke *et al.*[9] conducted a study on BP, which involved the utilization of intramedullary fixation, bone grafting, and, in certain instances, external fixation with ZA infusion. Following a period of 5.5 mo on average (4 to 7 mo), primary healing was observed in 6 out of 8 individuals. This study suggests that BP medication may be efficacious in preserving BMP-induced bone development by preventing osteoclastic bone loss, as evidenced by the primary healing observed in 6 out of 8 cases in the clinical data. Bisphosphonates have been employed to reduce osteoclasts due to the identification of elevated osteoclastic activity in the hamartomatous tissue adjacent to the pseudoarthrosis. The researchers employed BMP and documented favorable rates of integration.[23]

Das *et al.*[15] found that in the long term for people with Crawford type IV CPT and NF1, K-wire fixation alone compares favorably with K-wire fixation. The administration of rh-BMP facilitated prompt initial healing of primary fractures among patients in Group 1, although the results were not statistically significant. rhBMP-7 was preferred over BMP-2 due to its superior efficacy in promoting osteogenesis in NF1-deficient animals, as reported in previous studies.[22]

Based on the description above, it can be concluded that the role of BMP is more effective when combined with BP (ZA). These roles include being able to significantly increase the bone volume of the fusion mass, achieving complete tibial fusion, and achieving comprehensive cross-fusion between the tibia and fibula. In addition, BP play a role in maintaining BMP-induced bone development by preventing osteoclastic bone loss. Administration of ZA as well as rhBMP-2 not only showed no adverse effects and did not show any fractures during follow-ups of up to 7 yr. The BMP-2 itself has a positive effect on healing chronic non-union without causing adverse effects. As a result, the use of these two pharmacological drugs could be an option or alternative for CPT disease other than surgery.

However, this study has certain limitations, primarily the limited availability of literature examining the roles of BP and BMP in CPT disease. Consequently, the authors are unable to delineate the specific contributions of BP and BMP independently. It is hoped that further research can find more varied literature so that it can complement this research. In addition, close monitoring of the dosage is therefore essential. The potential influence of limited sample size, varied methodologies, and diverse dosages on the outcomes of the study warrants comprehensive elucidation. Future research should consider conducting a comparative analysis of BP dosages and delivery methods while also increasing the sample size to enhance the validity of the findings.

CONCLUSION

This study conducted a systematic review of six relevant articles and found that the use of BMPs combined with BP may serve as an effective adjuvant for surgery. This combination therapy has the potential to increase the rate of bone fusion, increase bone volume and fusion mass, and prevent bone refracture. Therefore, in addition to surgery, the use of pharmaceutical medications may be an option to CPT. It is important to be careful when administering these components to prevent unfavorable outcomes or adverse consequences such as fractures or complications.

ACKNOWLEDGEMENTS

We would like to thank all of our colleagues who helped us produce this manuscript.

REFERENCES

1. Bayusentono S, Brevi Putri T. Congenital pseudoarthrosis tibia in child with neurofibromatosis type 1 treated with the combined vascularized fibular graft and elastic stable intramedullary nail (Esin). J Orthop Traumatol Surabaya 2020; **9**(22): https://doi.org/10.20473/joints.v9i1.2020.22-28
2. Agrawal U, Vivek T. Congenital tibial pseudarthrosis. StatPearls. in NCBI Bookshelf 2022. 1-30.
3. Hissnauer TN, Stiel N, Babin K, Rupprecht M, Hoffmann M, Rueger JM, *et al*. Bone morphogenetic protein-2 for the treatment of congenital pseudarthrosis of the tibia or persistent tibial nonunion in children and adolescents: A retrospective study with a minimum 2-year follow-up. J Mater Sci Mater Med 2017; 28(4):60. https://doi.org/10.1007/s10856-017-5868-9
4. Patil SN, Rao PS, Yalamanchili RK. Residual nonunion in a case of two and a-half year old child congenital pseudarthrosis of ipsilateral tibia and fibula treated by intramedullary fixation with k-wire and allogenic cancellous strut graft: a case report. Int J Med Res Heal Sci 2013; 2(2):284-9. https://doi.org/10.5958/j.2319-5886.2.2.011
5. Khan T, Joseph B. Controversies in the management of congenital pseudarthrosis of the tibia and fibula. Bone Joint J 2013; 95-B(8):1027-34. https://doi.org/10.1302/0301-620X.95B8.31434
6. Shah H, Rousset M, Canavese F. Congenital pseudarthrosis of the tibia: management and complications. Indian J Orthop 2012; 46(6):616-26. https://doi.org/10.4103/0019-5413.104184
7. Laufer A, Fromer A, Gosheger G, Roedl R, Schiedel F, Broeking JN, *et al.* Reconstructive approaches in surgical management of congenital pseudarthrosis of the tibia. J Clin Med 2020; 9(12):4132. https://doi.org/10.3390/jcm9124132
8. Paley D. Congenital pseudarthrosis of the tibia: combined pharmacologic and surgical treatment using biphosphonate intravenous infusion and bone morphogenic protein with periosteal and cancellous autogenous bone grafting, tibio-fibular cross union, intramedullary. Bone Grafting 2012. https://doi.org/10.5772/31149
9. Birke O, Schindeler A, Ramachandran M, Cowell CT, Munns CF, Bellemore M, *et al.* Preliminary experience with the combined use of recombinant bone morphogenetic protein and bisphosphonates in the treatment of congenital pseudarthrosis of the tibia. J Child Orthop 2010; 4(10):507-17. https://doi.org/10.1007/s11832-010-0293-3
10. Pannier S. Congenital pseudarthrosis of the tibia. Orthop Traumatol Surg Res 2011; 97(7):750-61.

https://doi.org/10.1016/j.otsr.2011.09.001
11. Paley D. Congenital pseudarthrosis of the tibia: biological and biomechanical considerations to achieve union and prevent refracture. J Child Orthop 2019; 13(2):120-33. https://doi.org/10.1302/1863-2548.13.180147
12. Fabeck L, Ghafil D, Gerroudj M, Baillon R, Delincée P. Bone morphogenetic protein 7 in treating congenital pseudarthrosis of the tibia. J Bone Joint Surg Br 2006; 88(1):116-8. https://doi.org/10.1302/0301-620X.88B1.16619
13. Lee FYI, Sinicropi SM, Lee FS, Vitale MG, Roye DP, Choi IH. Treatment of congenital pseudarthrosis of the tibia with recombinant human bone morphogenetic protein-7 (rhBMP-7). A report of five cases. J Bone Jointt Surg Am 2006; 88(3):627-33. https://doi.org/10.2106/JBJS.D.02201
14. Bobyn J, Rasch A, Kathy M, Little DG, Schindeler A. Maximizing bone formation in posterior spine fusion using rhBMP-2 and zoledronic acid in wild type and NF1 deficient mice. J Orthop Res 2014; 32(8):1090-4. https://doi.org/10.1002/jor.22628
15. Das SP, Ganesh S, Pradhan S, Singh D, Mohanty RN. Effectiveness of recombinant human bone morphogenetic protein-7 in the management of congenital pseudoarthrosis of the tibia: A randomised controlled trial. Int Orthop 2014; 38(9):1987-92. https://doi.org/10.1007/s00264-014-2361-7
16. El-Hoss J, Chong T, Carpenter EC, Sullivan K, Deo N, Mikulec K, *et al.* A combination of rhBMP-2 (recombinant human Bone Morphogenetic Protein-2) and MEK (MAP kinase/ERK kinase) inhibitor PD0325901 increases bone formation in a murine model of neurofibromatosis type I pseudarthrosis. J Bone Joint Surg Am 2014; 96(4):e117. https://doi.org/10.2106/JBJS.M.00862
17. Papanna MC, Saldanha KA, Kurian B, Fernandes JA, Jones S. The use of recombinant morphogenic protein-2(rhBMP-2) in children undergoing revision surgery for persistent non-union. Strategies Trauma Limb Reconstr 2016; 11(1):53-8. https://doi.org/10.1007/s11751-016-0251-9
18. Deo N, Cheng TL, Mikulec K, Peacock L, Little DG, Schindeler A, *et al.* Improved union and bone strength in a mouse model of NF1 pseudarthrosis treated with recombinant human bone morphogenetic protein-2 and zoledronic acid. J Orthop Res 2018; 36(3):930-6. https://doi.org/10.1002/jor.23672
19. Shannon CE, Huser AJ, Paley D. Cross-union surgery for congenital pseudarthrosis of the tibia. Children 2021; 8(7):547. https://doi.org/10.3390/children8070547
20. Taqwin, Sumiaty, Lasman K. Penyuluhan, pengetahuan dan sikap pasangan usia subur tentang inspeksi visual asam asetat (IVA) di Kelurahan Birobuli. Poltekita J Ilmu Kesehat 2018; 12(1):8-14.
21. Wulandari FI, Susanti LW. Peningkatan sikap wanita usia subur tentang iva test melalui penyuluhan kesehatan. Infokes J Ilm Rekam Medis dan Inform Kesehat 2018; 8:16-20.
22. Butler RJ, Marchesi S, Royer T, Davis IS. The effect of a subject-specific amount of lateral wedge on knee mechanics in patients with medial knee osteoarthritis. J Orthop Res Sept 2007; 25(9):1121-7. https://doi.org/10.1002/jor.20423
23. Richards BS, Oentgen ME, Johnston CE. The use of rhBMP-2 for the treatment of congenital pseudarthrosis of the tibia: a case series. J Bone Joint Surg Am 2010; 92(1):177-85.

https://doi.org/10.2106/JBJS.H.01667
24. Carlier A, Geris L, Gastel NV, Carmeliet G, Oosterwyck HV. Oxygen as a critical determinant of bone fracture healing-A multiscale model. J Theor Biol 2015; 365:247-64. https://doi.org/10.1016/j.jtbi.2014.10.012
25. Cho TJ, Seo JB, Lee HR, Yoo WJ, Chung CY, Choi IH. Biologic characteristics of fibrous hamartoma from congenital pseudarthrosis of the tibia associated with neurofibromatosis type 1. J Bone Joint Surg Am 2008; 90(12):2735-44. https://doi.org/10.2106/JBJS.H.00014