

# Polydeoxyribonucleotide, as a Novel Approach for the Management of Medication-Related Osteonecrosis of the Jaw: A Preliminary Observational Study

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**Purpose:** Polydeoxyribonucleotide (PDRN), consisting of a mixture of deoxyribonucleotide polymers, has been suggested to have anti-inflammatory effects and enhance angiogenesis as an adenosine A<sub>2A</sub> receptor agonist. The aim of this study was to report the effectiveness of PDRN as an adjuvant therapy after surgical debridement in MRONJ (medication-related osteonecrosis of the jaw) patients.

**Materials and Methods:** Five patients (1 male, 4 females, age 65~79 years) who were diagnosed with MRONJ stage 2 or 3 underwent surgical debridement and PDRN mucosal injection. After surgical debridement, patients were subject to daily injection with 1 ml of PDRN around the surgical wound for 14 days.

**Result:** The patients' symptoms gradually disappeared. The surgical wound uneventfully healed, and no recurrence was observed during the follow-up period.

**Conclusion:** Although further studies are required, the present study first describes the possibility of PDRN as a useful option for MRONJ treatment.

**Key Words:** Medication-related osteonecrosis of the jaw; Polydeoxyribonucleotide

## Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is now a well-known complication of anti-

resorptive and antiangiogenic agents, such as bisphosphonates, denosumab (human monoclonal antibody to the receptor activator of nuclear factor kappa-B ligand [RANKL]) and sunitinib (tyrosine

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kinase inhibitor)<sup>1)</sup>. Numerous studies have been published to explore its nature and manage the disease. However, a reliable treatment regime has not been established. Although surgical approaches including surgical debridement and resective surgery are reported to be useful<sup>2,3)</sup>, it is also difficult to determine clean surgical margin<sup>4)</sup>. Since securing clean margin is known to be crucial to prevent recurrence, the extent of surgery tends to become wider, which in turn increases surgical morbidity. Therefore, various experimental and conservative approaches, such as low-level laser therapy, hyperbaric oxygen, PENT-E, teriparatide, platelet-rich fibrin, have been suggested to manage MRONJ<sup>5-9)</sup>. However, the effectiveness is not yet definite, hence, it may be wise to accompany surgical approaches especially when MRONJ class 2 or 3 is diagnosed<sup>2,3)</sup>.

Polydeoxyribonucleotide (PDRN), consisting of a mixture of deoxyribonucleotide polymers, has been suggested to have anti-inflammatory effects and enhance angiogenesis<sup>10-12)</sup>. The pharmacological action as an adenosine A<sub>2A</sub> receptor agonist following the cleavage by active cell membrane enzymes has shown to reduce inflammatory cytokines. In addition, up-regulation of vascular endothelial growth factor (VEGF) by stimulation of adenosine A<sub>2A</sub> receptor was also reported<sup>11,13)</sup>.

The aim of this study was to report the effectiveness of PDRN as an adjuvant therapy after surgical debridement in MRONJ patients. Although the

conservative surgical intervention reduces surgical morbidity, it still has disadvantage to leave acellular necrotic bone around the bony resection margin. Moreover, it is regarded as a dentoalveolar surgery which is one of the trigger factor of MRONJ. Therefore, we aimed to observe if PDRN can facilitate would healing process reducing the recurrence of the disease after conservative surgical debridement.

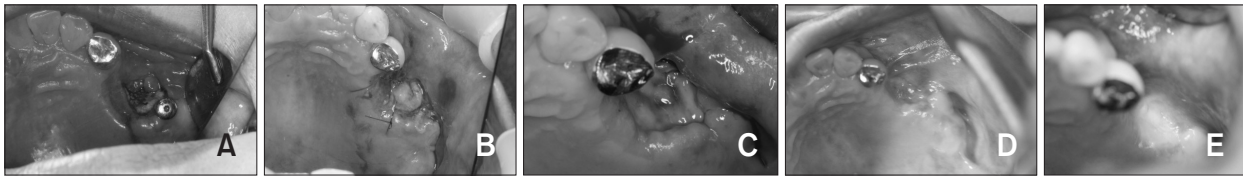
## Materials and Methods

Five patients (1 male, 4 females, age 65~79 years) who were diagnosed with MRONJ stage 2 or 3 were subjected to the treatment of surgical debridement and PDRN (Rejuvenex; Pharma Research Products, Seoul, Korea) mucosal injection at the Department of Oral and Maxillofacial Surgery of Kyung Hee University Dental Hospital at Gangdong between 2017 and 2018 (Table 1). Four patients had a history of taking oral bisphosphonates for the management of osteoporosis, and one patients received methotrexate because of rheumatoid arthritis. Clinically they had an exposed bone area. A sequestrum and/or a radiolucent lesion was also observed on a cone-beam computed tomography image. Surgical debridement of exposed bone area was performed until the bleeding points of remaining bone were confirmed. Afterwards, patients were subject to daily injection with 1 ml of PDRN around the surgical wound for 14 days. They were prescribed oral amoxicillin and clavulanic acid (375 mg) for three times daily

**Table 1.** Demographic data of the patients and their follow-up result

Patient no.	Sex	Age (yr)	Medication and duration (mo)	Location of lesion	ONJ classification	Bone exposure (1 mo f/u)	Bone exposure (6 mo f/u)	Clinical symptom (1 mo f/u)
1	M	69	Alendronate, 48	Lt. maxilla	Stage 2	None	None	None
2	F	79	Methotrexate, 50	Lt. mandible	Stage 2	None	None	None
3	F	65	Alendronate, 60	Rt. maxilla	Stage 2	None	None	None
4	F	77	Ibandronate, 71	Rt. mandible	Stage 2	None	None	None
5	F	79	Alendronate, 34	Rt. mandible	Stage 3	None	None	None

M: male, F: female, Lt.: left, Rt.: right, ONJ: osteonecrosis of the jaw, f/u: follow-up.



**Fig. 1.** Clinical photographs showing surgical wounds. (A) Preoperative photograph. (B) Immediate postoperative. (C) Ten days postoperative. (D) One-month postoperative. (E) Six months postoperative.

before admission, and intravenous amoxicillin and clavulanic acid (1 g) for three times daily after admission. Oral antimicrobial rinse (chlorhexidine 0.12% rinse) were also used until the completion of wound healing.

## Result

After the 2 weeks of PDRN injection, all patients demonstrated relief of pain and no sign of infection was noted. Soft tissue healing was progressive (Fig. 1). At 1-month follow-up, exposed bone area no longer existed for all patients (Table 1). Complete soft tissue coverage was obtained at the operation area. During the follow-up (range, 5~14 months), no recurrence was noticed both clinically and radiographically.

## Discussion

Surgical treatment is a reliable option for the management of MRONJ. However, inflammation and infection have been shown to contribute to the development of the disease<sup>14,15</sup>. Therefore, it is reasonable to speculate a possibility of recurrence after surgical treatment, especially following the conservative rather than radical resection. Nevertheless, the conservative surgical therapy has an advantage in terms of meeting patients' esthetic demand and proposing available prosthetic options. In order to apply the conservative surgical debridement with less risk of morbidity, a therapeutic approach that can be used as an adjuvant treatment should be considered.

Recently, PDRN has gained attention for its anti-inflammatory effect and resultant increase in vascularization. Various studies have been conducted to analyze the effect of PDRN. It decreased inflammatory cytokine secretion<sup>12,16</sup>, and increased various growth factors including fibroblast growth factor, VEGF, and transforming growth factor  $\beta$ <sup>17-19</sup>. Therefore, it is now utilized for inflammatory diseases, accelerating wound healing process<sup>20,21</sup>.

PDRN also showed its effect on macrophage cells treated with zoledronate and lipopolysaccharide (LPS)<sup>10</sup>. LPS had a synergetic effect together with zoledronate, reducing cell viability. However, supplement of PDRN increased cell viability and decreased inflammatory cytokines. After surgery, surgical wound is exposed to bacterial LPS in oral environment, and it is considered to increase the risk of MRONJ.

Therefore, this study was planned to see if PDRN also can be used for the management of MRONJ. Given that the conservative surgical treatment for MRONJ contains the risk of recurrence, we presumed that PDRN might reduce the risk and improve wound healing. PDRN was daily injected around the surgical wound. Subsequently patients' symptoms gradually disappeared. The wound uneventfully healed, and no recurrence was observed during follow-up period.

This result is in line with other studies. Kang et al.<sup>18</sup> reported improved tendon healing following Achilles tendon injury in rats. The tendon area repaired was significantly increased and the tensile strength of the tendon was also more resistant than the control group. In the study of Kim et al.<sup>22</sup>,

PDRN improved peripheral tissue oxygenation and inflammation in diabetic foot ulcers.

Although this study does not contain control group for comparison, it describes the possibility of PDRN as a useful option for MRONJ treatment as the first. After surgical treatment, wound healing is usually slow and sometimes troublesome due to recurrence. For these reason, local injection of PDRN local injection may deserve attention in MRONJ cases.

## Conclusion

Although further studies are required to confirm the result of this study, the present study suggests PDRN as a useful option for MRONJ treatment to accelerate wound healing and reduce the recurrence of osteonecrosis.

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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