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## EFFECTIVENESS OF RECOMBINANT BONE MORPHOGENETIC PROTEIN rhBMP-2 USE IN ATYPICAL THIRD MANDIBULAR MOLARS EXTRACTION

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**Abstract. Effectiveness of morphogenetic protein rhBMP-2 use in atypical third mandibular molars extraction.**

**Gudaryan O.O., Idashkina N.G., Nekhanevich Zh.M.** *Objective – improving the effectiveness of treatment of patients with retention and dystopia of the third molars of the lower jaw in their horizontal or inverse position by developing an integrated approach using photodynamic therapy and drugs that enhance osteogenesis (platelet autoplasm enriched with i-PRF fibrin and recombinant morphogenetic protein (rhBMP-2)). 82 patients with difficult eruption of third molars of the lower jaw aged 19 to 37 were included in research: 40 (48.8%) men and 42 (51.2%) women. The standard approach to performing operations of atypical removal of retained third molars causes a significant number of complications (large bone defects, inflammatory contracture, post-traumatic neuritis, etc.). Treatment process was provided in two stages. During the first (preoperative) stage sanitation was done to eliminate or stabilize an acute infection which is inflammatory process in the area of impacted third molar. The second stage provides abscessed tooth extraction, wound sanitation, formed defect filling with osseo-inductive medications under the collagen membrane and complete closure. The developed surgical method for treating retention and dystopia of the lower third molars using biomaterial based on demineralized bone matrix (BCP) saturated with recombinant morphogenetic protein of bone rhBMP-2 can reduce the occurrence of postoperative inflammatory complications by 35.4%, and also reduce the time for their elimination as well.*

**Реферат. Ефективність застосування морфогенетичного білка кістки rhBMP-2 при атиповому видаленні третіх молярів нижньої щелепи.** Гудар'ян О.О., Ідашкіна Н.Г., Неханевич Ж.М. *Мета роботи – підвищення ефективності лікування хворих з ретенцією і дистопією третіх молярів нижньої щелепи при їх горизонтальному або інверсному положенні за допомогою розробки комплексного підходу з використанням фотодинамічної терапії та препаратів, що підсилюють остеогенез (тромбоцитарної аутоплазми, збагаченої фібрином і-PRF і рекомбінантного морфогенетичного білка (rhBMP-2)). У дослідження включено 82 пацієнти у віці від 19 до 37 років. Серед них 40 (48,8%) чоловіків і 42 (51,2%) жінки. У всіх пацієнтів були встановлені ознаки утрудненого прорізування третіх молярів нижньої щелепи (перикоронарит, флегмона, лімфаденіт), дистопія, дефіцит місця. Стандартний підхід у проведенні операції атипового видалення ретинованих третіх молярів зумовлює значну кількість ускладнень (великі кісткові дефекти, запальні зміни, контрактури жувальних м'язів та суглобів, посттравматичний неврит, інфекційні ускладнення). Лікування проводилося в два етапи. На першому етапі (передопераційному) здійснювалася санація оперативної зони, спрямована на ліквідацію або купірування гострого інфекційно - запального процесу в ділянці ретинованого третього моляра. Другий етап передбачав видалення причинного зуба, санацію рани і заповнення утвореного дефекту остеоіндуктивними препаратами під колагенову мембрану й ушивання рани наглухо. Розроблений хірургічний метод лікування ретенції і дистопії нижніх третіх молярів із застосуванням біоматеріалу на основі демінералізованого кісткового матриксу (BCP), насиченого рекомбінантним морфогенетичним білком кістки rhBMP-2, дозволяє знизити виникнення післяопераційних запальних ускладнень на 35,4%, а також скоротити терміни їх ліквідації.*

Despite the progress in treatment modes of impaction and dystopia of the third mandibular molars, the incidence of postoperative complications connected with complex abnormal extraction remains sufficiently high [4]. The reasons are anatomic dentition features as well as complexity and traumatism of surgical measures, stipulated by acinal or inverse direction of dentition third of mandibular molars. Increase of extent of operation leads to major bone defects, to repair which special conditions are required [2, 9].

Currently the osteal wound care principles are formed. They are based on the creation of the aseptic conditions of filling of defect with the full blood clot that provides agenesis process within the primary union. With the heavy bone losses the present approach does not always allow to prevent the development of early postoperative complications, connected with contamination of injury, complicates further bone loss reactivation [10].

In order to prevent inflammatory complications in pre- and postoperative period different anti-infective external (antiseptic) and general (antibiotic) drugs are used. Despite their broad spectrum of action, at the moment of extremely traumatizing impacted third mandibular molars extraction the number of complications varies from 14 to 55% [1]. Thus, the search for effective methods of surgical wound sanitation is relevant.

Therefore photodynamic therapy is of interest for the study. Recently, given type of treatment plays the leading role in the infection elimination, affecting on the focus of infectious inflammatory process. The method is proved to contribute to destruction of bacterium cellular structure and elimination of local humoral immunity deficiency and potentiates microcirculatory processes.

The management of reparative osseogenesis optimization requires further development and in-depth study. It allows to achieve early recovery of three-dimensional bone defects, formed after the impacted third mandibular molar extraction. In recent decade Boda S.K., Almoshari Y. administer the calcium binding bone morphogenetic protein (BMP-2) to solve the given problem, regulatory peptide to reactivate paradontium and osseous structures [6]. This is one of the most advantageous directions in the implementation of the specific materials in medical practice. Schorn L, Sproll C study results show that the pattern of rhBMP-2 and VEGF topically applied with the collagenous agent leads to the three-dimensional osteogenesis in single-step in vivo procedure [12]. Gomes-Ferreira P.H., Okamoto R. concluded that in case of big defects compounds including recombinant BMP (rhBMP-2), allograft bone and PRP (plasma-rich platelet) can be used as osseous tissue substitutes [8]. Jeyaraj P.E., Chakranarayan A. in their works show that PRF (platelet-rich fibrin) and its fractions administration in post-extraction defects is high-value management which provides quick soft tissues postoperative cicatrization with minimal complications (postoperative edema, pain, trismus) and osteo-regenerative process as well [5, 7].

Meanwhile, questions of these drugs administration, administration ways into the bone defects, frequency of usage for the patients with third mandibular molars impaction and dystopia are still open and require solutions.

Study object – the object of the study is treatment improvement of the patients with acinal or inverse third mandibular molar impaction and dystopia within the development of integrated approach with photodynamic therapy and drugs administration

improving osseogenesis (platelet-rich plasma, enriched with fibrin i-PRF and recombinant morphogenetic protein (rhBMP-2).

#### MATERIALS AND METHODS OF RESEARCH

82 patients with difficult third mandibular molars eruption at the age from 19 to 37 were enrolled into the complex clinic-based, laboratory, radiological investigation. There were 40 (48,8%) male subjects and 42 (51.2%) female subjects. All patients had invariable indications for impacted third mandibular molar extraction like difficult wisdom tooth eruption (pericoronitis, phlegmon, lymphadenitis), dystopia, space shortage.

At the beginning of treatment process every patient, taking part in the study, was informed and then consented to take part in the research (Declaration of Helsinki, 2013). Investigation was approved by the commission for biomedical ethics of State Establishment "Dnipropetrovsk Medical Academy of Health Ministry Ukraine" No 2 from 10.02.2017. Healthy patients with diagnosed according to ICD-10 third molar abnormality (K-07.35 impacted teeth with improper mandibular angle and mandibular ramus) were selected for the study. 64 (83.9%) patients were diagnosed with horizontal type of eruption with medial angulation and 8 (16.1%) patients with vertical type of eruption with mesial angulation.

Difficult eruption in the cohort was followed by inflammatory complications the most common of which was acute pericoronitis in 61 patients (74.4%) and rarely – chronic one in 21 patients (25.6%).

Patients with cardiovascular diseases, respiratory infections, endocrine diseases, gastrointestinal diseases, persistent infection foci of the adjacent teeth as well as allergic states in anamnesis were not enrolled into the study.

Treatment process was provided in two stages. During the first (preoperative) stage sanitation was done to eliminate or stabilize an acute infection which is inflammatory process in the area of impacted third molar. The second stage provided abscessed tooth extraction, wound sanitation, formed defect filling with osseo-inductive medications under the collagen membrane and complete closure.

Clinic-based study was conducted according to the standard practice. Patient's locals and overall status, complaints, anamnestic data were analyzed in details. Oral cavity tissues as well as unbiased clinical signs which show mucosa state in the third molar zone were examined.

Orthopantomography data were used to evaluate topographic-anatomic features of impacted/misplaced third mandibular molars. Orthopantomograms were done on the apparatus PlanmecaProOne

(firm «Planmeca», Finland) under conditions: 60-75 kW, 7 mA with timing at 10 seconds. Further, state of alveolar bone, dentition, reparative regeneration dynamics were studied with the help of computerized tomography on the tomograph PlanmecaProFace (firm «Planmeca», Finland). Following image processing was carried with the use of Planmeca Romexis Viewer 4.4.1.R program package («Planmeca», Finland) that enables to calculate mean value in units of Hounsfield (units H or Hounsfield Units or HU) representing the bone density.

Microbiocenosis research was done by a classical microbiologic approach with the detection of quantitative and species composition of aerobic and anaerobic flora. Sampling from the difficult third mandibular molar eruption area in the preoperative period was with a sterile paper point, while in a postoperative period sampling from mucosa in the area of surgical intervention was with nominal sorbing tampon. Further, turunda or tampon tail-piece was lavaged in 10 ml of saline solution to collect microbe magma. Biological material inoculation of medium was done in the laboratory settings.

Culturing was conducted in aerobic and anaerobic conditions at the temperature of 37°C. Anaerobic organism culture was done in aerostat for 5-7 days. Bacteria identification was conducted by the morphological, cultural, biological properties with the use of API (France) and BBL Cristal System (USA) test kit. Microbe sampling material patterns are given in the Table 1. In most of the cases aerobic-anaerobic associations (with two-three associations) were identified.

All patients underwent preoperative preparation with sanitation of infection inflammatory retromolar area. To achieve these goals HELBO therapy (HELBO Photodynamic system) was used. Professional hygienic measures were conducted under the application of Lidocaine Solution 10.0% (chronic pericoronitis) or block anesthesia with Sol. Ultracaini 4%-1.7 ml (acute pericoronitis), after which damage area was filled with photosynthetase following by laser irradiation with exposure dose up to 3 min. The procedure was repeated during 3-5 days till complete, evident control or marked decline of inflammatory manifestations and soft tissues oedema abolition or decrease in the area of difficult third mandibular molar eruption. Since that surgical treatment stage starts [11].

Surgical intervention was performed by the united protocol in all patients. Under block and infiltration anesthesia with Sol. Ultracaini 4%-1.7 ml L-type incision of mucosa and peri-osteum in retromolar area from pterygoid- mandibular area along alveolar crest of the gum to the second

mandibular molar, continuing it along the vestibular mandibular surface to the second molar according to the inflection of the mandibular body. After incision mucoperiosteal graft was cut. Osteotomy was conducted with the use of ball-shaped dental cutter

following by continuous cooling with the saline solution. After the third molar exposure, extraction was being done with a straight elevator. During this procedure all patients developed great bone losses with partial damage of inter-alveolar septum.

Table 1

**Incidence of bacterial population detection in patients with different forms of pericoronitis**

| Microbe species and genus  | Microbe detection rate ratios (%) |                  |
|----------------------------|-----------------------------------|------------------|
|                            | pericoronitis, n=82               |                  |
|                            | acute phase                       | inveterate phase |
| Staphylococcus aureus      | 26/61                             | 4/21             |
| Streptococcus spp.         | 22/61                             | 2/21             |
| Streptococcus intermedius  | 12/61                             | 2/21             |
| Staphylococcus epidermidis | 14/61                             | 3/21             |
| Streptococcus viridans     | 12/61                             | 4/61             |
| Peptostreptococcus spp.    | 19/61                             | 6/21             |
| A. Actinomycetem comitans  | 8/61                              | 4/21             |
| Prevotella intermedia      | 14/61                             | 3/21             |
| Porphyromonas gingivalis   | 20/61                             | 6/21             |
| Bacteroides forcythus      | 14/61                             | 4/21             |
| Fusobacterium nucleatum    | 12/61                             | 3/21             |
| Candida albicans           | 18/61                             | 8/21             |
| Enterococcus spp.          | 8/61                              | 4/21             |

Post-operative wound curettage was made with photodynamic exposure with HELBO system. Further, depending on osteal wound care, referral to osseogenesis was performed in 3 groups with the usage of different methods.

20 patients were enrolled into the first group, they were administrated with the standard technique for the given abnormality. After the third molar extraction bone loss was filled with blood clot and the wound was sutured tightly.

Patients of the second group (31 people) had their osseous tissue defect replaced with the osteoplastic material BioOss (Switzerland) mixed with i-PRF in the ratio 2:1.

The third group consisted of 31 patients. After impacted/misplaced third mandibular molar extraction bone loss was filled with biomaterial based on the demineralized bone matrix (BCP), imbued with

recombinant bone morphogenetic protein rhBMP-2 in the ratio 3:1. On the second, third and fourth day after the operation all patients were administrated HELBO therapy according to the technology described above.

Statistical analysis of material was conducted with the use of program for statistical processing Statistica 6.1 (serial number AGAR909E415822FA), EXCEL 2010 (license number 02260-018-0000106-48794) with average mean calculation (M), standard mean square errors of arithmetic middling (m), Student coefficient. Differences were considered reliable at  $p < 0.05$  [3].

**RESULTS AND DISCUSSION**

After preoperative preparation, it was detected earlier reversal of infectious inflammatory process clinical features in retromolar area in inveterate pericoronitis than in acute course. Full regress of



clinical symptoms of chronic inflammation was already detected among 78 patients (98,0%) after 2, 3 HELBO therapy manipulations. Mucosa a round impacted/misplaced third mandibular molar gains pale pink color, on palpation is anodynous. 4 treated patients (5%) with evident acute suppurative inflammation of soft tissues had inflammatory process eliminated only to the end of 5 manipulations.

Preoperative preparation duration in patients with acute pericoronitis continued not less than 5-6 days and not all subjects were followed with full sanitation of inflammatory process in retromolar area. Despite performed treatment, 49 (80.3%) patients had acute pericoronitis eliminated but the rest 12 (18.7%) patients had clinical features retained, although they significantly reduced. It is worth noting that HELBO therapy usage at the preoperative preparation stage contributed to abolition of gingival tissue edema as well as pyorrhea from inflammation foci.

Pronounced clinical effect of HELBO therapy in patients with inveterate and acute pericoronitis was

combined with full elimination of infectious inflammatory process in retromolar area. On completion of treatment manipulations involving photodynamic irradiation in material, taken directly from 7 (33.3%) patients with inveterate pericoronitis and from 45 (73.8%) patients with acute pericoronitis in the impacted/misplaced third mandibular molars area, Peptostreptococcus, Prevotella, Bacteroides were not detected. Together with anaerobic microflora from the sites of damage, such aerobes as staphylococcus, streptococcus (Str. Intermedius, Str. Aureus, Str. Haemolyticus) were defined. In 8% of patients with inflammation only certain agents of the above microbes were detected after HELBO therapy. General opportunistic bacteria content reduced from Lg 8.2±0.6 to Lg 1.6±0.3 but full sanitation was not achieved. It was demanded to administer a subsidiary antibiotic therapy for the given patients (Amoxiclav 250 mg 3 times a day) with a course for 6 days.

Table 2

**HELBO therapy effect on the microflora of patients with different forms of pericoronitis (on the third day)**

| Microbe species and genus  | Microbe detection rate ratios (%) |                  |
|----------------------------|-----------------------------------|------------------|
|                            | pericoronitis, n=82               |                  |
|                            | acute phase                       | inveterate phase |
| Staphylococcus aureus      | 3/61                              | 1/21             |
| Streptococcus spp.         | 2/61                              | 1/21             |
| Streptococcus intermedius  | 3/61                              | 1/21             |
| Staphylococcus epidermidis | 3/61                              | 0/21             |
| Streptococcusviridans      | 2/61                              | 1/61             |
| Peptostreptococcus spp.    | 0/61                              | 0/21             |
| A. Actinomycetem comitans  | 0/61                              | 0/21             |
| Prevotella intermedia      | 0/61                              | 0/21             |
| Porphyromonas gingivalis   | 1/61                              | 0/21             |
| Bacteroides forcythus      | 0/61                              | 0/21             |
| Fusobacterium nucleatum    | 1/61                              | 0/21             |
| Candida albicans           | 2/61                              | 0/21             |
| Enterococcus spp.          | 1/61                              | 1/21             |

It should be noted that microbiocenosis recovery in retromolar area as well as further increased rate and inoculation of gingival tissue with obligate bacteria (Bifid bacteria, Lactic acid bacillus, Str. Veridans) happened on the 3<sup>rd</sup>-4<sup>th</sup> day after HELBO therapy manipulations. Impacted/misplaced third mandibular molar extraction was conducted in these time limits.

Clinical research in the earliest time limits after the usage of different modes of surgical management and remedial treatment in conditions of «pure» operation zone (with impacted/misplaced third mandibular molars) better results in representatives of the second and third groups were detected. During 2-3 days after the operation, acute spontaneous pain was registered more often among the patients from the 1<sup>st</sup> group (4 patients (20.0%) but critical edema and tissue hyperemia around the wound was detected in 13 patients (65.0%) of the 1<sup>st</sup> group, 9 patients (29.0%) – of the 2<sup>nd</sup> group and 5 patients (16.1%) – of the 3<sup>rd</sup> one. An inflammatory contracture, during the first three days was defined in 11 patients (55.0%) of the 1<sup>st</sup> group, 12 patients (38.7%) of the 2<sup>nd</sup> group and 9 patients (29.0%) of the 3<sup>rd</sup> one. Enlarged, algescic regional lymphatic nodes were detected in 20,0% of the first group patients, in 12.5% of the second group patients and in 6% of the third group patients who were operated according to our processed method.

Final analysis of the postoperative medical data research showed that the long-term inflammatory complications in 45.0% of the patients administrated conventional treatment (I group) and in 25.8% of

patients who had their bone loss replaced with autoblood osteoplastic material rich with i-PRF (II group) were observed quite frequently, in 9.6% of patients who were treated with the use of the mixture based on recombinant morphogenetic protein (rhBMP-2) above complications were very rare. It is characteristic that complications appeared after the third mandibular molar extraction were resolved in different terms: in III group patients by 2-3 day of treatment (on average 6.2±0.3), this process was a bit longer in II group – up to 3-4 days (on average 8.6±0.2) and up to 5-6 days in patients administrated conventional treatment (on average 11.4±0.3).

Computer densitometric examination data evaluation of patients from all groups made in remote terms (in 3, 6 and 12 months) after the third mandibular molar extraction showed that osseous tissue regenerative process in patients treated by the conventional treatment methods and by our methods was different. It is detected that osseous tissue reversibility in the extracted tooth zone has the intense course in patients whose bone loss was replaced with osteoplastic material in combination with recombinant morphogenetic protein (rhBMP-2). It was proved by the dynamics of density rise according to Hounsfield scale (table 3). At the end of 3, 6 and 12 months osseous tissue density reversibility in the first group patients who had third mandibular molars extracted and conventionally treated, was by 1.02; 1.01 and 1.03 times less than in II group patients and by 1.06; 1.06 and 1.05 times less comparing with the III group (Table 3).

Table 3

**Dynamics of changes of osseous tissue density in the area of impacted / misplaced third mandibular molar in the study group patients according to Hounsfield scale (M±m)**

| Study groups      | Mineral density indicants of osseous tissue according to Hounsfield scale |                                  |                                  |
|-------------------|---------------------------------------------------------------------------|----------------------------------|----------------------------------|
|                   | 3 months                                                                  | 6 months                         | 12 months                        |
| I (21 patients)   | 341.6±13.5                                                                | 359.3±13.2<br>p3<0.05            | 374.4±12.6<br>p3<0.05            |
| II (31 patients)  | 350.8±15.2<br>p1<0.05                                                     | 361.5±13.2<br>p1<0.05<br>p3<0.05 | 384.3±14.8<br>p1<0.05<br>p3<0.05 |
| III (31 patients) | 373.4±16.5<br>p2<0.05                                                     | 383.9±12.8<br>p2<0.05<br>p3<0.05 | 402.9±13.4<br>p2<0.05<br>p3<0.05 |

Notes. p 1 – statistical significance relative to the I group data; p 2 – statistical significance relative to the II group data; p 3 – statistical significance relative to the previous stage.

Thus, comparative study of the received medical, radiological and microbiologic data detected essential advantages of the offered surgical method of treatment of impaction and dystopia of third mandibular molars with pericoronitis in preoperative period. This method involves photodynamic effect and postoperative bone loss replacement with osteoplastic material in combination with recombinant morphogenetic protein (rhBMP-2) in contrast to the conventional treatment. It is established that these results were caused by the multifactorial manipulations of our treatment complex aimed at the infectious inflammatory process sanitation in retromolar area, any kinds of complications prophylaxis as well as reduction of the osseo-regeneration period. As the result we have full reversibility of the damaged tissue. All mentioned above allows to recommend this surgical method of impaction and dystopia of third mandibular molars with pericoronitis for the widespread use in surgical dental practice treatment.

There has been a lack of consensus on the operational effectiveness at the time of atypical third mandibular molar extraction. Many authors call for studies under strict standardized conditions [1, 6], but we have received additional data about effectiveness of morphogenetic protein rhBMP-2. The agreement considering the terms of treatment of patients with damage to the third mandibular molar

was not achieved either [2, 7]. Results of current study have shown effectiveness of therapy schedule.

### CONCLUSIONS

1. An administration of photodynamic therapy to patients with impaction and dystopia of third mandibular molars with pericoronitis in preoperative period promotes quick elimination of infectious inflammatory process in retromolar area which makes conditions for the further operative therapy of the given abnormality.

2. Developed surgical treatment of third mandibular molar impaction and dystopia with the use of biomaterial based on the demineralized bone matrix (BCP), imbued with recombinant bone morphogenetic protein rhBMP-2 in the ratio 3:1 allows to decrease postoperative inflammatory complications by 35.4%, reduce elimination period (on average up to 5.2 days). Also it improves graft quality in the postoperative defects area according to CT scan in by 1.07 times in 3 months; by 1.08 times in 6 months and by 1.09 times in 12 months.

3. Computer radiological densitometry method gives an opportunity to conduct postoperative monitoring of reparative osseogenesis dynamics in the area of extracted impacted/ misplaced third mandibular molar.

Conflict of interests. The authors declare no conflict of interest.

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