Title
The effects of Nd:YAG laser hemostasis on pain and wound healing after tooth extraction: A split-mouth randomized controlled clinical trial

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The effects of Nd:YAG laser hemostasis on pain and wound healing after tooth extraction: A split-mouth randomized controlled clinical trial

by
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Dedication and Acknowledgements

To my co-resident and wife, Sepi, for her endless love and support.

To Drs. Shigemi Nagai, Masazumi Nagai, and John Da Silva who have shaped me (with sushi) to the scholar I am today.

To my siblings and parents who have had to deal with me their entire life.

The effects of Nd:YAG laser hemostasis on pain and wound healing after tooth extraction: A split-mouth randomized controlled clinical trial

Cliff Lee

Abstract

Tooth extraction is a common surgical procedure that includes severing hard and soft tissue to remove the tooth from its alveolar bony housing. Following extraction, normal stages of wound healing occur, including pain and inflammation, proliferation, and maturation. The aim of this study was to evaluate the effect of laser hemostasis on pain and soft tissue healing following tooth extraction. Ten patients who were referred for simple premolar extractions for orthodontic reasons participated in the study, for a total of 32 sites. Sites were randomly allocated to control or intervention group. Following simple tooth extraction, buccolingual (BL) and mesiodistal (MD) measurements were made, and the intervention sockets received treatment from an Nd:YAG laser on the "hemostasis" setting in contact mode (4W, 1064 nm, 20 Hz, 515 µs pulse duration). Patients were given routine post-operative instructions, as well as a pain assessment survey to be completed day 1, 2, 3, and 7 following the procedure. Additional measurements were made at one- and two-week follow up. Overall, there was low reported pain following tooth extraction on all days and no complications noted. Significantly faster soft tissue healing occurred in the laser group in both BL and MD dimension at one week, and in the MD direction at two weeks. Faster soft tissue healing occurred in the laser group in the BL dimension at two weeks but did not reach statistical significance. Future studies are needed with more patients and more complex extractions to further elucidate the benefits of laser therapy following tooth extraction.

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I. Introduction and Background

Tooth extraction is a common surgical procedure that includes severing hard and soft tissue to remove the tooth from its alveolar bony housing. Reasons for tooth extraction include, but are not limited to, tooth decay, endodontic infection, periodontal disease, for orthodontic treatment, pericoronitis, pathology, and prophylactic removal of third molars. Postoperative pain is a common symptom that accompanies nearly all extractions including simple tooth extractions.[1] Other morbidity associated with tooth extraction includes alveolar osteitis, swelling, infection, trismus, and nerve damage, and are even more common in traumatic or complicated surgeries such as impacted third molar extractions.[2,3] Because of this, prescription analgesic medications such as opioids are routinely prescribed following dental extraction procedures. Although non-opioid medications are very effective for pain management after dental procedures,[4–6] dentists are still a significant source of opioid prescriptions, contributing to the current opioid epidemic national public health emergency.[7,8] Thus, methods other than analgesics that can reduce post-operative morbidity by intervening in the natural events following tooth extractions warrant exploration.

1.1 Healing events in an extraction socket

The first and perhaps the most important event following tooth extraction is the formation of a fibrin clot.[9,10] A stable fibrin clot is essential for the prevention of epithelial downgrowth,[11–13] which allows for bone rather than soft tissue to eventually fill into the socket. Following the formation of a fibrin clot, granulation tissue replaces the fibrin clot. Connective tissue begin to appear by the fourth day in the periphery of the socket, and move centrally, replacing the most central granulation tissue around the twentieth day. During this time, around the seventh day, bone formation begins with the appearance of osteoids at the base of the socket.[10] Epithelialization over the surface of the socket occurs at a rate of 0.5 to 1 mm a day,[14] although complete fusion and maturation of the epithelium does not occur until 24 to 35 days. Bone maturation takes longer, typically 12 to 16 weeks for initial remodeling and maturation.[15]

1.2 Post-operative morbidity

Postoperative pain is the most common symptom that accompanies nearly all extractions including simple tooth extractions, due to the normal inflammatory cascade and release of pro-inflammatory cytokines following injury and subsequent wound healing.[1,16] Alveolar osteitis, also known as dry socket, is a common complication that causes significant pain and discomfort for an extended amount of time that is not adequately relieved by analgesics.[17] It is caused by a failure of a stable clot formation or breakdown of the fibrin clot inside the socket, likely due to fibrinolytic activity caused by microorganisms or damaged alveolar bone cells, which can lead to exposed and denuded bone.[18] Risk factors for alveolar osteitis include smoking, use of oral contraceptives, poor oral hygiene, active or recent gingival infection or pericoronitis, and difficult or deeper impactions of third molars.[17] Other routine complications and morbidity include swelling and trismus, especially for third molar extractions, especially when significant bone needs to be removed.[19] More significant complications and morbidity following extractions include nerve damage and osteonecrosis of the jaw in patients with history of bisphosphonate use and radiation therapy.

1.2.1 Current methods for reducing post-operative morbidity

There have been many studies exploring methods for reducing post-operative morbidity after extractions. Because alveolar osteitis may have a microbial component, eliminating putative pathogens can reduce the amount of fibrinolytic activity and help to keep a stable clot. Indeed, local and systemic antibacterial agents such as antibiotics or chlorhexidine can significantly reduce the incidence of alveolar osteitis.[17,20–23] Platelet rich plasma and platelet rich fibrin have been used in extraction sockets to fortify the fibrin clot and concentrate growth factors to induce fibroblast activity,[24] and have been shown to reduce pain and improve soft tissue healing,[25–29] and even swelling and trismus.[30] Corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce the robustness of the inflammatory cascade response can reduce pain, swelling, and improve range of motion.[19,31–34]

1.3 Lasers in medicine and surgery

The use of lasers in medicine and surgery was first described by Goldman in 1961 for the treatment of skin melanoma and by Trokel in 1963 for a corneal surgery.[35,36] Since then, lasers have become an important asset in the armamentarium for many medical fields, including ophthalmology, dermatology, surgery, periodontology, oral and maxillofacial surgery, and operative dentistry.[36–44] Its widespread adoption owes to the versatility and array of properties that lasers can have depending on the desired application. In order to obtain the desired effects, one must consider the following factors on laser-tissue interactions: the irradiated tissue and the laser radiation/properties.

1.3.1 Irradiated tissue

When tissue is irradiated, the interactions can be divided into a primary optical/spectral response, and secondary responses such as photochemical or photothermal interaction (typically the generation of heat), photoablation, plasma-induced ablation, and photodisruption. Optical responses can include absorption, reflection, scattering, transmission, and refraction. Absorption occurs when the light stops at the object and is transformed to a different type of energy. Reflection occurs when light bounces off the surface at the same angle as the incoming light. In contrast, scattered light bounces off in many different directions. Transmission occurs when light moves through an object unchanged, and refraction when light changes direction and/or speed as it moves through an object.

Absorption, reflection, and scatter are the dominant effect on opaque surfaces while absorption, transmission, and refraction are the dominant effect on translucent surfaces. Secondary responses depend on the radiation intensity and interaction time. High intensity in a short time causes ablation, or vaporization, either with thermal changes as in photoablation, or without as in plasma induced ablation and photodisruption. With less intensity and longer interaction time, photothermal and photochemical interactions are more likely. Coagulation and hemostasis are examples of a photothermal interaction in different proteins that may be desired in tissue surgery.

The targeted tissue can vary considerably depending on application. Hard tissue typically includes bone, enamel, dentin, and cementum. The differences in these components can be simplified into the amount of water and hydroxyapatite in each. Soft tissue typically includes skin, muscle, vessels, and adipose tissue. The main chromophores, component that absorbs specific radiation wavelength, for soft tissue are water, melanin, and hemoglobin.

1.3.2 Laser radiation and properties

The wavelengths generated by the lasers correspond to the amount of energy per photon and can be divided into infrared, visible, ultraviolet, and X-rays. Different wavelengths correspond to different relative absorptions by different tissue components (**Figure 1**). As such, the wavelength for the laser chosen is vital depending on the application. Because water is present in most tissue, any wavelength with high absorption of water could be utilized as a universal tissue laser. For a more targeted approach, wavelengths such as those around the infrared spectrum between 700 nm to 1000 nm have absorption in melanin and hemoglobin and none with water.

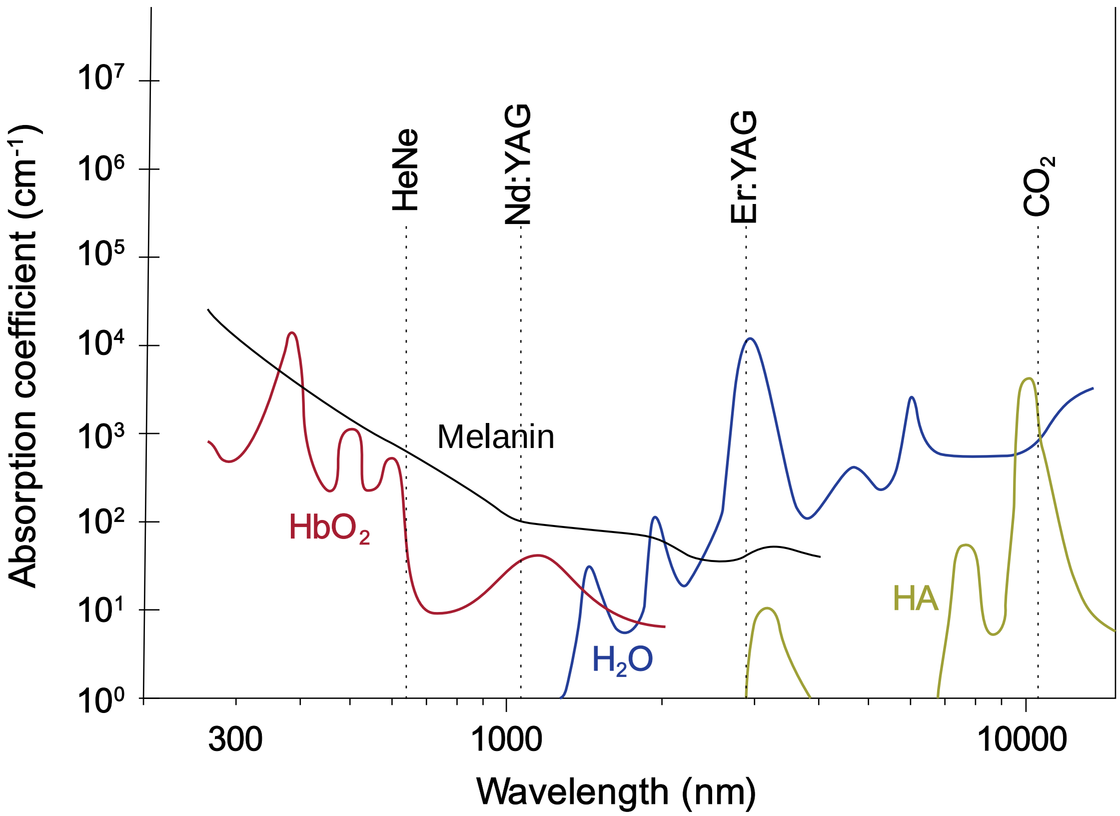


Figure 1: Absorption spectra of components found in oral hard and soft tissue.

Common chromophores include oxygenated hemoglobin (HbO_2), melanin, water (H_2O), and hydroxyapatite (HA). Wavelengths of lasers commonly used in medicine and dentistry are presented showing tissue absorption coefficients for the corresponding wavelengths.

The temporal characteristics of lasers depend on the pumping mechanism (continuous or pulsed) as well as the working regime (free-running, Q-switched, or mode-locked). The time characteristics determine the duration of tissue exposition as well as the power of the radiation.

The class of lasers can be broadly categorized by the gain medium, the type of medium used to amplify optical power. These include solid-state, semiconductor, gas, and liquid lasers.

Popular solid-state lasers used currently in medicine and surgery include neodymium-doped lasers such as the Nd:YAG, erbium laser such as the Er:YAG and Er:Cr:YSGG, and the alexandrite lasers like the $Cr^{3+}:BeO.Al_2O_3$. Semiconductor lasers are better known as diode lasers. Common gas lasers include CO_2, Argon, and HeNe lasers.

The most commonly used lasers in periodontal soft tissue surgery in dentistry are the Er:YAG, Nd:YAG, and diode lasers. The Er:YAG laser operates at a wavelength of 2940 nm, which has a high absorption by water (**Figure 1**). Because water is present in soft tissue, bone, and teeth, the Er:YAG is absorbed by all tissue and thus is considered a universal and superficial/shallowly penetrating laser. In contrast, most diode lasers operate at the 800-1000 nm wavelength, similar to the Nd:YAG at 1064 nm, which have no absorption with water and high absorption with melanin/pigmentation (**Figure 1**). This makes diode and Nd:YAG lasers more deeply penetrating and more specific to pigmented tissue. Tissue ablation and hemostasis occurs directly from absorbance of Er:YAG laser energy, whereas emitted light is converted to heat to create a “hot tip” in diode and Nd:YAG lasers to coagulate and vaporize tissue. All three lasers allow for precise incision of soft tissue with some degree of hemostasis which is beneficial for soft tissue surgery.

Out of the three lasers, the Nd:YAG produces the thickest coagulation layer and hemostasis due to its deeper penetration.[38] Because of the deeper penetration, the laser energy can biostimulate the surrounding tissue to induce angiogenesis and fibroblasia. Biostimulation with the Nd:YAG has been successfully used to treat osteonecrosis following tooth extraction in patients taking bisphosphonates.[45,46] The Nd:YAG has well documented success in periodontal treatment for laser-assisted new attachment procedure (LANAP) through regeneration of periodontal tissue due to its ability to produce a stable fibrin clot as well as its bactericidal properties.[38,47–49] The laser used in LANAP is the Periolase® MVP-7™, which is a 6-watt, free-running variable pulsed, Nd:YAG laser (Millenium Dental Technologies, Cerritos, CA). Depending on the indication for use, the wattage and pulse duration can be changed; high power in a short amount of time is indicated for ablation, longer pulse duration with lower power is indicated for hemostasis. Given these properties, we hypothesize that the Nd:YAG laser can be used to decrease the post-operative pain and complications following tooth extractions, as well as increase the speed of wound healing.

II. Materials and Methods

The protocol of this study was reviewed and approved by the Institutional Review Board of the University of California San Francisco (IRB#: 18-25290) and was conducted in full accordance with the Declaration of Helsinki of 1975, as revised in 2008.

2.1 Subject selection

The study population for the present split-mouth randomized controlled clinical trial consisted of patients who were referred to the University of California San Francisco (UCSF) Dental Center Periodontology Clinic for simple premolar extractions for orthodontic treatment from October 2018 to January 2020. Patients were included if they were systemically healthy, at least 9 years old, and required at least two premolar extractions on the same arch crossing the midline as prescribed by a dentist for orthodontic treatment. Patients were excluded if the teeth were severely crowded or rotated, or if the extractions included flap elevation, bone removal, tooth sectioning, ridge grafting with bone or bone-substitutes or membranes, sinus or nerve exposure in the surgical wound. Patients were also excluded if they were taking anticoagulants, antibiotics, analgesics, NSAIDs, corticosteroids, or other medications for medical conditions, patients with a known history of bleeding diathesis.

2.2 Clinical procedure

All extractions were performed under local anesthesia by various periodontal residents at UCSF, but the laser treatment and measurements were completed by a single operator. Prior to the procedure, one site was randomly allocated to the control and the other as the treatment site. After the extraction procedure, the Periolase® MVP-7™ (Millenium Dental Technologies, Cerritos, CA) was used on the "hemostasis" setting in contact mode (4W, 1064 nm, 20 Hz, 550 μs pulse duration), starting from the apex of the socket, and moving around the walls of the socket circumferentially and coronally until a thick fibrin clot was present in the socket, approximately 30 seconds for the entire socket. In the control socket, the same movements were mimicked with the laser, but without the laser activated. Prior to being dismissed, patients were given routine post-operative instructions regarding oral hygiene and diet and given sterile gauze to bite on for 20 minutes.

2.3 Measurements

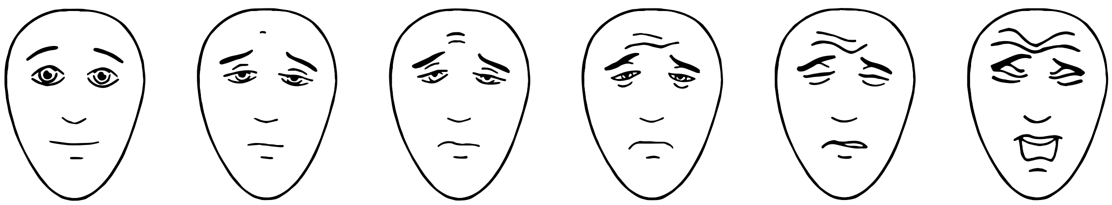
Measurements were taken of the extraction sockets immediately after the clinical procedure by a single operator before the laser treatment was completed. Immediately after the laser treatment, intraoral photos were taken. Measurements and intraoral photos were also taken at the one-week follow-up, and a two-week follow-up. Buccolingual (BL) and mesiodistal (ML) dimensions were measured at the widest point of the most coronal aspect of the socket using curved Castroviejo Calipers (Hu Friedy, Chicago, IL). Patients were also given four pain assessment forms and instructed to complete the forms in the morning before taking any analgesics on days 1, 2, 3, and 7 after the procedure. The pain assessment forms consisted of a six-point Likert scale based on the validated Faces Pain Scale-Revised (FPS-R, **Figure 2**).[50,51]

2.4 Statistical analysis

All analyses were performed using a statistical software package (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Because of the lack of independence with site-level data collection from different patients, comparison of healing and pain by laser treatment or control were made with the generalized estimating equations (GEE) method assuming an exchangeable correlation structure. Age, gender, arch, and side were explored as potential confounders in a multiple GEE regression model.

These faces below show how much something can hurt. The face on the furthest left (0) shows no pain. The face on the furthest right (10) shows very much pain.

Please circle the face AND write down the face number that shows how much you hurt right now on your **LEFT** side.



0 2 4 6 8 10

The face that shows how much I hurt right now on my **LEFT** side is face number _______.

Figure 2: Sample of the pain assessment form

III. Results

Ten patients with a total of 32 sites were included in the study. Demographic data and distribution of extractions are shown in **Table 1**. Clinical procedures and wound healing were uneventful with no complications, such as alveolar osteitis or uncontrolled bleeding, reported.

Table 1: Patient population and extraction site characteristics

No. of patients	10
No. of sites	32
Female/male	8/2
Mean age (range)	188 months (119 – 451)
Maxilla/mandible	18/14
Right/left treatment	6/10

3.1 Pain

Overall, reported pain was low after the extractions, with the highest mean pain of 3.25 on Day 1 and pain was virtually nonexistent by Day 7 (**Figure 3**, **Table 2**). The only case of high pain was an outlier (**Figure 4**). There was no statistical difference between the laser and control groups for all time points ($p>0.05$).

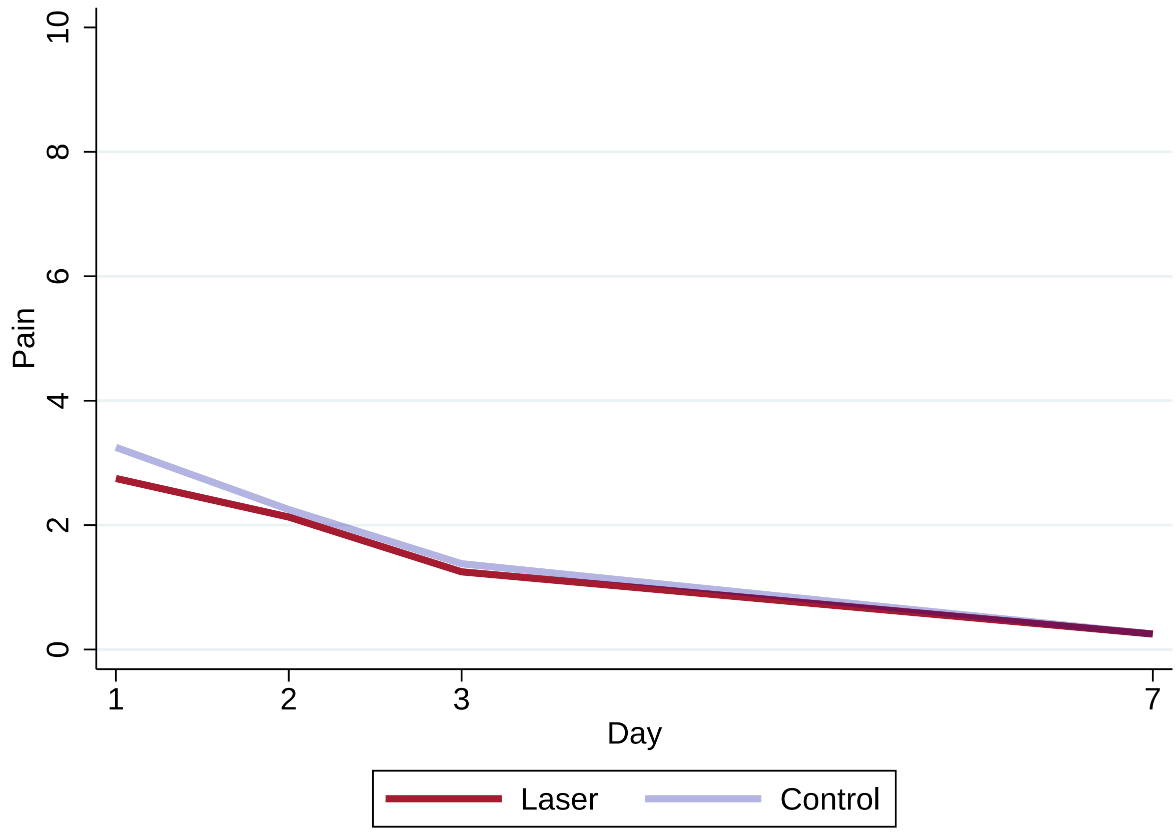


Figure 3: Reported pain over time in laser and control groups after extraction.

Table 2: Reported pain for laser and control sites after extraction.

Mean numbers are shown with standard deviation in parenthesis on a scale of 0 to 10 based on FPS-R.

	Day 1	Day 2	Day 3	Day 7
Laser	2.75 (2.79)	2.13 (3.03)	1.25 (2.04)	0.25 (0.68)
Control	3.25 (2.96)	2.25 (2.96)	1.38 (2.03)	0.25 (0.68)

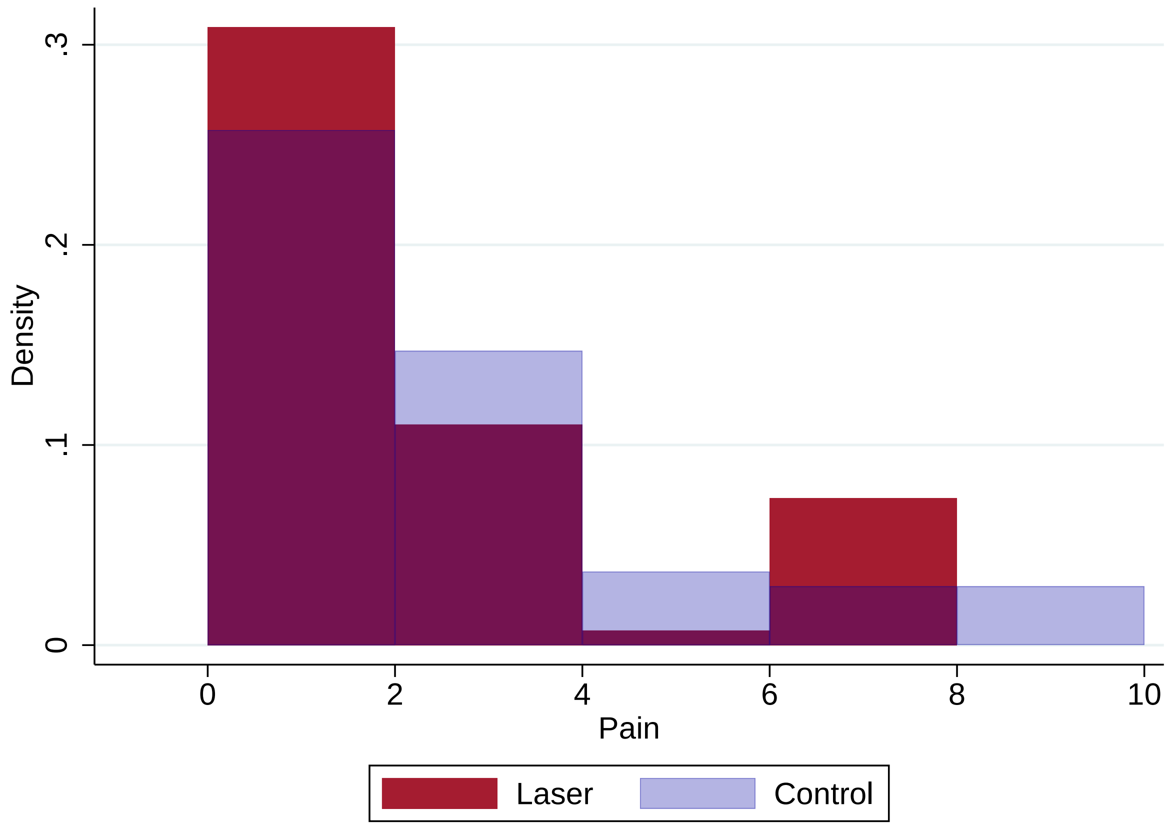


Figure 4: Frequency density of reported pain after extraction

3.2 Healing

Table 3 shows the soft tissue healing at weeks one and two in both BL and MD dimensions as calculated from the initial socket dimensions. The laser group showed higher tissue healing in both dimensions at both time points.

Table 3: Initial socket dimensions and soft tissue healing at one and two weeks.

Mean numbers are shown with standard deviation in parenthesis.

	Day 0: BL	Day 0: MD	Week 1: BL	Week 2: BL	Week 1: MD	Week 2: MD
Laser	8.75 mm (0.29)	5.43 mm (0.24)	42.4% (14.7)	49.6% (13.2)	46.7% (12.5)	55.3% (12.2)
Control	8.66 mm (0.34)	5.52 mm (0.20)	30.6% (17.1)	41.4% (16.9)	30.1% (16.2)	41.1% (14.9)

Examples of healing in the laser and control groups are shown in **Figure 5**. A stable fibrin clot is visible after using the laser for hemostasis (**Figure 5A**), whereas no fibrin clot has formed yet in the control group, and the blood has not coagulated (**Figure 5C**). After one week of healing, the laser site still has a layer of fibrin in the coronal aspect protecting the socket (**Figure 5B**), while the control group has an immature matrix of granulation and connective tissue in the apical aspect of the socket (**Figure 5D**).

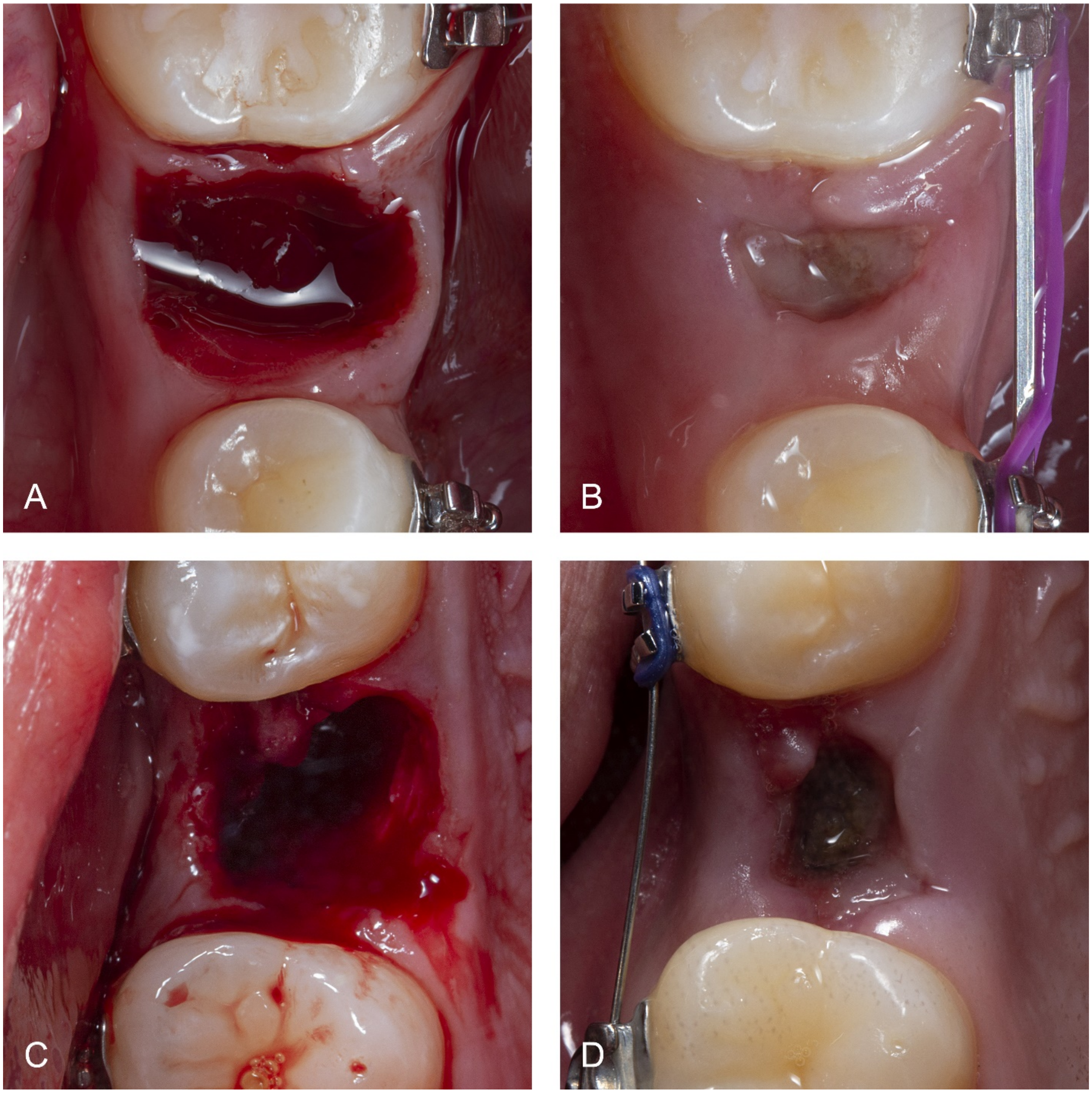


Figure 5: Intraoral photographs of healing sockets

(A) Laser-treated socket immediately post-op. A thick fibrin clot is visible in the socket after laser hemostasis. (B) Laser-treated socket at 1-week post-op. A fibrin layer is still intact on the coronal portion of the socket. (C) Control site immediatelys post-op. Hemostasis has not yet been achieved. (D) Control site at 1-week post-op. An immature matrix of granulation and connective tissue at the apical portion of the socket is visible.

To further investigate the role of laser treatment in healing, a multiple GEE regression model was fit, with adjustments for age, gender, arch, and side as covariates. However, none were found to contribute significantly to the model and was dropped. **Table 4** shows the results of the GEE model. Laser treatment had a positive odds ratio for all dimensions and time points and was significantly associated with improved healing in the BL dimension at one week, and the MD dimension for both one and two week recalls.

Table 4: GEE logistic regression for relationship of laser treatment and healing

† denotes 95% confidence interval. * denotes statistical significance.

	Odds Ratio	95% CI†	P-value
Week 1 – BL			
Non-laser	1.00		
Laser	1.12	1.03, 1.23	<0.01*
Week 2 – BL			
Non-laser	1.00		
Laser	1.08	0.95, 1.25	0.195
Week 1 – MD			
Non-laser	1.00		
Laser	1.18	1.12, 1.24	<0.001*
Week 2 – MD			
Non-laser	1.00		
Laser	1.15	1.01, 1.33	0.037*

IV. Discussion

There has been a growing interest in investigating the use of lasers as adjuncts for various clinical applications. In particular, lasers have been well studied in non-surgical and surgical periodontal therapies.[38,41,44,47–49] As innovations of non-pharmacological methods for decreasing morbidity after surgery grow, investigating lasers to treat post-extraction sockets is important.

In our split-mouth randomized clinical trial, pain and healing were assessed after using the PerioLase® MVP-7™ Nd:YAG laser for hemostasis in post-extraction sockets. The effect of the laser on soft tissue healing was positive in all samples, with an increased healing in all dimensions at both the one- and two-week post-operative visit. The GEE model allows for analysis when combining both site-level and patient-level data, in which there may be a lack of independence. For example, certain patients may have a far more significant response to the laser, so taking multiple sites from those patients could have more “weight” if only site-level data were considered. The GEE model showed significant positive odds ratio on healing associated with laser treatment in both BL and MD dimensions at one week, and the MD dimension at two weeks. The model did not quite reach statistical significance for the BL at two weeks. Because of scheduling difficulties, less patients and sites were available for the two-week follow up, causing the sample size and thus the variation in results to be higher. This is likely the reason that the GEE model did not quite reach statistical significance for BL healing at two weeks, but still showed a moderate effect on the healing.

The increased soft tissue healing seen in the laser groups validate the importance of a stable fibrin clot in wound healing. Using the laser to induce hemostasis produced a demonstratable, physical coagulum immediately after laser treatment. The fibrin layer was often seen even at the one-week visit, providing protection, a nutrient source, and a matrix for healing to occur in the socket. Unfortunately, apico-coronal dimensions were not measured in this study, although the difference in the depth of the healing is visible in **Figure 5**, with the granulation tissue in the apical aspect of the socket and empty space occupying the coronal aspect of the socket for the control site. Previous experiments in periodontal wound healing have explored the effects when the fibrin clot was destabilized with heparin.[11–13] Those experiments found that repair and regeneration was inhibited with heparin, and that a stable and mature fibrin clot was the main factor for regeneration of the periodontium instead of epithelial migration. Based on these findings combined with those of this study, it would be interesting to investigate the long-term effects of laser-assisted hemostasis in post-extraction sockets, especially the effect on vital bone formation.

Pain was generally low and was practically non-existent after one week in both the laser and control group except for one outlier. The use of a validated pain scale in a young population helps ensure that the low reported pain is a reliable result. The reason for the low pain is likely related to the young cohort, with a mean age of 15.7 years who needed extractions for orthodontic treatment. Extractions in younger patients are typically considered easier,[52] largely because the bone in adolescents is more elastic.[53] This allows for expansion of the alveolus, and thereby an easier tooth extraction. The post-extraction sockets were from simple premolar extractions in healthy teeth with no signs of disease or infection. As a result, no complications such as alveolar osteitis were reported, and the post-operative pain was extremely low. Most patients were young, with a mean age of 15.7 years. Although age was not found to be a significant confounder, this is likely due to the limited range of ages included in the study.

Based on the results of this study, future studies are warranted to address the limitations previously mentioned. Specifically, including a broader age range of patients and more procedures, such as surgical extractions and impacted third molars, is needed. This would allow for greater opportunity to focus on morbidity and pain which were not seen in our study. In addition, expanding the scope of the study to include the effects on hard tissue, such as vital bone formation, and apico-coronal dimensional healing of soft tissue could yield valuable results.

V. References

1. Al-Khateeb TH, Alnahar A. Pain Experience After Simple Tooth Extraction. J Oral Maxillofac Surg. 2008;66(5):911–7.
2. Bui CH, Seldin EB, Dodson TB. Types, Frequencies, and Risk Factors for Complications after Third Molar Extraction. J Oral Maxillofac Surg. 2003;61(12):1379–89.
3. Friedman JW. The prophylactic extraction of third molars: A public health hazard. Am J Public Health. 2007;97(9):1554–9.
4. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: A qualitative review. Br J Anaesth. 2002;88(2):199–214.
5. Mehlisch DR. The efficacy of combination analgesic therapy in relieving dental pain. J Am Dent Assoc. 2002;133(7):861–71.
6. Denisco RC, Kenna GA, O'Neil MG, Kulich RJ, Moore PA, Kane WT, et al. Prevention of prescription opioid abuse. J Am Dent Assoc. 2011;142(7):800–10.
7. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in Opioid Analgesic Abuse and Mortality in the United States. N Engl J Med. 2015;372(3):241–8.
8. Steinmetz CN, Zheng C, Okunseri E, Szabo A, Okunseri C. Opioid Analgesic Prescribing Practices of Dental Professionals in the United States. JDR Clin Transl Res. 2017;2(3):241–8.
9. Amler MH, Johnson PL, Salman I. Histological and histochemical investigation of human alveolar socket healing in undisturbed extraction wounds. J Am Dent Assoc. 1960;61(1):32–44.

10. Amler MH. The time sequence of tissue regeneration in human extraction wounds. Oral Surgery, Oral Med Oral Pathol. 1969;27(3):309–18.

11. Wikesjö UME, Nilvéus RE, Selvig KA. Significance of Early Healing Events on Periodontal Repair: A Review. J Periodontol. 1992;63(3):158–65.

12. Wikesjö UME, Selvig KA. Periodontal wound healing and regeneration. Periodontol 2000. 1999;19(1):21–39.

13. Polimeni G, Xiropaidis A V., Wikesjö UME. Biology and principles of periodontal wound healing/regeneration. Periodontol 2000. 2006;41(1):30–47.

14. Engler WO, Ramfjord SP, Hiniker JJ. Healing following simple gingivectomy. A tritiated thymidine radioautographic study. I. Epithelialization. J Periodontol. 1966;37(4):298–308.

15. Evian CI, Rosenberg ES, Coslet JG, Corn H. The osteogenic activity of bone removed from healing extraction sockets in humans. J Periodontol. 1982;53(2):81–5.

16. Zhang J, An J. Cytokines, Inflammation, and Pain. Int Anesthesiol Clin. 2007;45(2):27–37.

17. Blum IR. Contemporary views on dry socket (alveolar osteitis): a clinical appraisal of standardization, aetiopathogenesis and management: a critical review. Int J Oral Maxillofac Surg. 2002;31(3):309–17.

18. Amler MH. Disturbed healing of extraction wounds. J Oral Implantol. 1999;25(3):179–84.

19. Markiewicz MR, Brady MF, Ding EL, Dodson TB. Corticosteroids Reduce Postoperative Morbidity After Third Molar Surgery: A Systematic Review and Meta-Analysis. J Oral Maxillofac Surg. 2008;66(9):1881–94.

20. Larsen PE. The effect of a chlorhexidine rinse on the incidence of alveolar osteitis following the surgical removal of impacted mandibular third molars. J Oral Maxillofac Surg. 1991;49(9):932–7.

21. Hermesch CB, Hilton TJ, Biesbrock AR, Baker RA, Cain-Hamlin J, McClanahan SF, et al. Perioperative use of 0.12% chlorhexidine gluconate for the prevention of alveolar osteitis: efficacy and risk factor analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85(4):381–7.

22. Fotos PG, Koorbusch GF, Sarasin DS, Kist RJ. Evaluation of intra-alveolar chlorhexidine dressings after removal of impacted mandibular third molars. Oral Surgery, Oral Med Oral Pathol. 1992;73(3):383–8.

23. Ragno JR, Szkutnik AJ. Evaluation of 0.12% chlorhexidine rinse on the prevention of alveolar osteitis. Oral Surg Oral Med Oral Pathol. 1991;72(5):524–6.

24. Albanese A, Licata ME, Polizzi B, Campisi G. Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration. Immun Ageing. 2013;10(1):23.

25. Alissa R, Esposito M, Horner K, Oliver R. The influence of platelet-rich plasma on the healing of extraction sockets: an explorative randomised clinical trial. Eur J Oral Implantol. 2010;3(2):121–34.

26. Rutkowski JL, Fennell JW, Kern JC, Madison DE, Johnson DA. Inhibition of alveolar osteitis in mandibular tooth extraction sites using platelet-rich plasma. J Oral Implantol. 2007;33(3):116–21.

27. Rutkowski JL, Johnson DA, Radio NM, Fennell JW. Platelet rich plasma to facilitate wound healing following tooth extraction. J Oral Implantol. 2010;36(1):11–23.

28. Arenaz-Búa J, Luaces-Rey R, Sironvalle-Soliva S, Otero-Rico A, Charro-Huerga E, Patiño-Seijas B, et al. A comparative study of platelet-rich plasma, hydroxyapatite, demineralized bone matrix and autologous bone to promote bone regeneration after mandibular impacted third molar extraction. Med Oral Patol Oral Cir Bucal. 2010;15(3):e483-9.

29. Eshghpour M, Dastmalchi P, Nekooei AH, Nejat A. Effect of platelet-rich fibrin on frequency of alveolar osteitis following mandibular third molar surgery: A double-blinded randomized clinical trial. J Oral Maxillofac Surg. 2014;72(8):1463–7.

30. Ogundipe OK, Ugboko VI, Owotade FJ. Can autologous platelet-rich plasma gel enhance healing after surgical extraction of mandibular third molars? J Oral Maxillofac Surg. 2011;69(9):2305–10.

31. Beirne OR. Corticosteroids decrease pain, swelling and trismus. Evid Based Dent. 2013;14(4):111.

32. Buyukkurt MC, Gungormus M, Kaya O. The effect of a single dose prednisolone with and without diclofenac on pain, trismus, and swelling after removal of mandibular third molars. J Oral Maxillofac Surg. 2006;64(12):1761–6.

33. Markovic A, Todorovic L. Effectiveness of dexamethasone and low-power laser in minimizing oedema after third molar surgery: a clinical trial. Int J Oral Maxillofac Surg. 2007;36(3):226–9.

34. Bamgbose BO, Akinwande JA, Adeyemo WL, Ladeinde AL, Arotiba GT, Ogunlewe MO. Effects of co-administered dexamethasone and diclofenac potassium on pain, swelling and trismus following third molar surgery. Head Face Med. 2005;1:11.

35. Trokel SL, Srinivasan R, Braren B. Excimer laser surgery of the cornea. Am J Ophthalmol. 1983;96(6):710–5.

36. Jelínková H. Lasers for Medical Applications: Diagnostics, Therapy and Surgery. Cambridge: Woodhead Publishing; 2013.

37. Svelto O. Principles of Lasers. Boston, MA: Springer US; 2010.

38. Aoki A, Mizutani K, Schwarz F, Sculean A, Yukna RA, Takasaki AA, et al. Periodontal

and peri-implant wound healing following laser therapy. Periodontol 2000. 2015;68(1):217–69.

39. Munnerlyn CR, Koons SJ, Marshall J. Photorefractive keratectomy: A technique for laser refractive surgery. J Cataract Refract Surg. 1988;14(1):46–52.

40. Pick RM, Colvard MD. Current Status of Lasers in Soft Tissue Dental Surgery. J Periodontol. 1993;64(7):589–602.

41. Romanos GE. Clinical applications of the Nd:YAG laser in oral soft tissue surgery and periodontology. J Clin Laser Med Surg. 1994;12(2):103–8.

42. Basford JR. Low intensity laser therapy: still not an established clinical tool. Lasers Surg Med. 1995;16(4):331–42.

43. Dawdy J, Halladay J, Carrasco-Labra A, Araya I, Yanine N, Brignardello-Petersen R. Efficacy of adjuvant laser therapy in reducing postsurgical complications after the removal of impacted mandibular third molars: A systematic review update and meta-analysis. J Am Dent Assoc. 2017;148(12):887-902.e4.

44. Mizutani K, Aoki A, Coluzzi D, Yukna R, Wang CY, Pavlic V, et al. Lasers in minimally invasive periodontal and peri-implant therapy. Periodontol 2000. 2016;71(1):185–212.

45. Vescovi P, Meleti M, Merigo E, Manfredi M, Fornaini C, Guidotti R, et al. Case series of 589 tooth extractions in patients under bisphosphonates therapy. Proposal of a clinical protocol supported by Nd: YAG low-level laser therapy. Med Oral Patol Oral Cir Bucal. 2013;18(4):1–6.

46. Vescovi P, Merigo E, Meleti M, Fornaini C, Nammour S, Manfredi M. Nd:YAG laser biostimulation of bisphosphonate-associated necrosis of the jawbone with and without surgical treatment. Br J Oral Maxillofac Surg. 2007;45(8):628–32.

47. Yukna R a, Carr RL, Evans GH. Histologic evaluation of an Nd:YAG laser-assisted new attachment procedure in humans. Int J Periodontics Restorative Dent. 2007;27:577–87.

48. Nevins ML, Camelo M, Schupbach P, Kim S-W, Kim DM, Nevins M. Human clinical and histologic evaluation of laser-assisted new attachment procedure. Int J Periodontics Restorative Dent. 2012;32(5):497–507.

49. Nevins M, Kim S-W, Camelo M, Martin IS, Kim D, Nevins M. A prospective 9-month human clinical evaluation of Laser-Assisted New Attachment Procedure (LANAP) therapy. Int J Periodontics Restorative Dent. 2014;34(1):21–7.

50. Bieri D, Reeve RA, Champion GD, Addicoat L, Ziegler JB. The faces pain scale for the self-assessment of the severity of pain experienced by children: Development, initial validation, and preliminary investigation for ratio scale properties. Pain. 1990;41(2):139–50.

51. Hicks CL, Von Baeyer CL, Spafford PA, Van Korlaar I, Goodenough B. The Faces Pain Scale - Revised: Toward a common metric in pediatric pain measurement. Pain. 2001;93(2):173–83.

52. Gbotolorun OM, Arotiba GT, Ladeinde AL. Assessment of Factors Associated With Surgical Difficulty in Impacted Mandibular Third Molar Extraction. J Oral Maxillofac Surg. 2007;65(10):1977–83.

53. Baroncelli GI, Federico G, Bertelloni S, De Terlizzi F, Cadossi R, Saggese G. Bone quality assessment by quantitative ultrasound of proximal phalanxes of the hand in healthy subjects aged 3-21 years. Pediatr Res. 2001;49(5):713–8.

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