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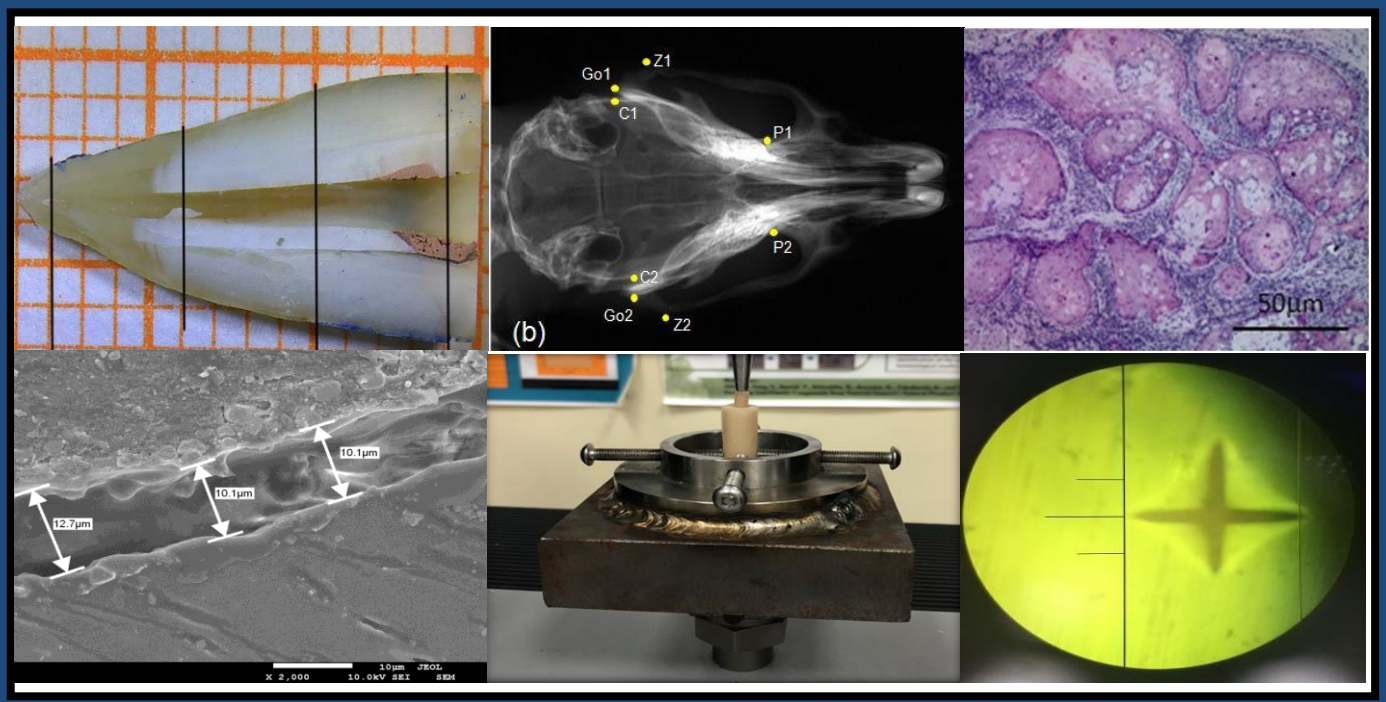

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JOURNAL OF INTERNATIONAL DENTAL AND MEDICAL RESEARCH

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2020; 13 (1)

DENTISTRY

EXPERIMENTAL ARTICLE

1. **Evaluation of the effectiveness of root canal obturation depending on the treatment methods**
   Taras V. Furtsev, Anastasya A. Kazanovskaya, Galina M. Zeer, Elena G. Zelenkova
   Pages 1-7

EXPERIMENTAL ARTICLE

2. **Biomarkers as Bioindicators to Early Detection of Pollution Effects in Environmental and the Human Health**
   Rrahman Ferizi, Nora Shabani, Arben Murtezani, Ragip Shabani, Naim Haliti, Fehim Haliti, Tibor Altenberger
   Pages 8-16

EXPERIMENTAL ARTICLE

3. **The Effect of Ginkgo Biloba (Egb) Extracts on the Expression of Hsp 90, Vegf and Bdnf in the Rattus Novergicus with Lead (Pb) Exposure**
   Muhammad Hamdan, Noorhamdani AS, Masruroh Rahayu, Mohammad Hasan Machfoed
   Pages 17-22

EXPERIMENTAL ARTICLE

4. **Compressive Strength Evaluation of Giomer and Compomer Storage in Different Media**
   Ali A. Razooki Al-Shekhli, Isra'a Al Aubi
   Pages 23-28

EXPERIMENTAL ARTICLE

5. **Effect of Post-Polymerization Microwave Treatment on Mechanical Properties and Dimensional Change of Provisional Self-Cure PMMA**
   Jamaporn Karawatthanaworrakul, Juthatip Aksornmuang
   Pages 29-35

EXPERIMENTAL ARTICLE

6. **Comparative Evaluation and Efficacy of Linezolid, Vancomycin and Ciprofloxacin on Enterococcal induced biofilm using Scanning Electron Microscopy an in vitro study**
   Musab Hamed Saeed, Manu Zacharias, Krishna Prasad Shetty, Alexender M Luke, Simy Mathew
   Pages 36-41

EXPERIMENTAL ARTICLE

7. **The Effect of Canal Preparation using 2Shape, ProTaper GOLD and ProTaper Next File Systems on the Fracture Resistance of Obturated Roots**
   Hadeel Rushdi Khdairah, Hikmet A. Al-Gharrawi
   Pages 42-45

EXPERIMENTAL ARTICLE

8. **Zinc Supplementation in Cytokine Regulation During LPS-induced Sepsis in Rodent**
   Martono T Utomo, Subijanto M Sudarmo, Ketut Sudiana
   Pages 46-50

EXPERIMENTAL ARTICLE

9. **Role of Fascin in Xenografted Tumorigenesis in Nude Mice: A Histological Study**
   Xianglan Zhang, Young Sun Hwang
   Pages 51-56

EXPERIMENTAL ARTICLE

10. **In Vitro Antifungal Effect of Biodentine™ Against Candida Albicans**
    Donika Bajrami, Miranda Stavileci, Agime Dragidella, Zana Sejfija
    Pages 57-60

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2020; 13 (1)

EXPERIMENTAL ARTICLE

11. **Expression of Il-1β in Periodontitis Post Oral Administration of Papaya Seed Extract**
Ratih Pusporini, Ahmad Basori, Agung Krismariono
Pages 61-66

EXPERIMENTAL ARTICLE

12. **Beverages Immersion Effect on Compomer and Giomer Microhardness**
Ali A. Razooki Al-Shekhli, Isra'a Al Aubi
Pages 67-72

EXPERIMENTAL ARTICLE

13. **Effect of Stichopus Hermanni to Remodeling Maxillary Suture Expansion on Craniofacial Structure and Teeth**
Noengki Prameswari, Henry Sebastian, Rahma Ariesti, Kristin Gaby Rosari, Kenny Rama Widya, Ela Amelia, Fatimah Batul, Fenny Felia, Flavia Pratamaningdyah, Pambudi Rahardjo, Lisdiana Mardanus, Sarianoferni, Emy Khoironi
Pages 73-79

EXPERIMENTAL ARTICLE

14. **Accuracy of Digital Periapical Radiography and Cone Beam Computed Tomography for Evaluation of Root Canal Configuration in Human Mandibular first Premolars**
Phiangfah Kongkiatkool, Peraya Puapichartdumrong, Weeraya Tantanapornkul, Thosapol Piyapattamin, Kessiri Wisithphrom
Pages 80-85

EXPERIMENTAL ARTICLE

15. **Enamel polishing after orthodontic bracket debonding using two different protocols and two different adhesives**
Hussein A. Alnajar, Hayder A. Kadhim
Pages 86-90

EXPERIMENTAL ARTICLE

16. **Acute Toxicity Test of Liquid Smoke of Rice Hull (Oryza sativa) on Mice (Mus Musculus)**
Ira Arundina, Tantiana, Indeswati Diyatri, Meircurius Dwi Condro Surboyo, Rachma Adityasari
Pages 91-96

EXPERIMENTAL ARTICLE

17. **Root Canal Preparation using Hyflex EDM/CM VS Revo S in Curved Root Canals, a Comparative in-vitro Study**
Maryam Kuzekanani, Ali Abbasi Sardari
Pages 97-100

EXPERIMENTAL ARTICLE

18. **Comparison of Reverse Torque in Different Types of Implant Screw Systems**
Tahir Karaman, Onur Evren Kahraman
Pages 101-105

EXPERIMENTAL ARTICLE

19. **Comparative Evaluation of Canal Preparation Time by Using Three Different Shape Memory Files –An In-Vitro Study**
R.Rajakeerthi, M.S. Nivedhitha
Pages 106-110

EXPERIMENTAL ARTICLE

20. **Irrigation Solution Pattern in Root Canal Treatment (Irrigation Solution Pattern in Root Canal between Negative Pressure System by Endovac and Sonic Activation by Eddy System)**
Dian Agustin Wahjuningrum, Raymond Kandow, M Rulianto, Kevin Prayogo
Pages 111-115

JIDMR
JOURNAL OF INTERNATIONAL DENTAL AND MEDICAL RESEARCH

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2020; 13 (1)

EXPERIMENTAL ARTICLE

21. **The Efficacy of D-Race and Different NiTi rotary Instruments in the Removal of Root Canal Filling Materials**
Mustafa Tariq Mutar, Iman Mohammed Al-Zaka
Pages 116-121

EXPERIMENTAL ARTICLE

22. **Inhibition of Streptococcus Mutans Growth Induced by the Extract of Citrus Aurantifolia Peel**
Jeffrey Jeffrey, Mieke Hemiawati Satari, Dikdik Kurnia, Sunarjati Sudigdoadi
Pages 122-127

EXPERIMENTAL ARTICLE

23. **Coronal Leakage of two Different Root Canal Sealers**
Tringa Kelmendi, Ferit Kocani, Blerim Krasniqi, Arsim Kurti, Blerim Kamberi
Pages 128-133

EXPERIMENTAL ARTICLE

24. **A High Sucrose Diet Affects Calcium Levels and the Number of Osteoblasts in the Wistar Rat Extraction Socket**
Christian Khoswanto
Pages 134-137

EXPERIMENTAL ARTICLE

25. **Antibody Induced by Porphyromonas Gingivalis FimA-PVXCP DNA Vaccine Inhibit Host Cell Invasion and Enhance Phagocytosis**
Jantipa Jobsri, Nattachai Saiwarin, Thanit Prasitsak, Warayut Chotprakaikiet, Kusuma Jamdee, Niratcha Chaisomboon
Pages 138-143

EXPERIMENTAL ARTICLE

26. **Hyperbaric Oxygen Therapy Effect on Androgen Receptor and Superoxide Dismutase in Insulin-Resistant Polycystic Ovary Syndrome**
Budi Santoso, Widjiati, Ahmad Syaifuddin Zuhri, Firas Farisi Alkaff
Pages 144-148

EXPERIMENTAL ARTICLE

27. **Marginal Fit of Metal Copings Fabricated from Digital and Conventional Impression Methods: an In Vitro Study**
S Simna, M Sheejith, Sukumaran Anil
Pages 149-154

EXPERIMENTAL ARTICLE

28. **Effectiveness of Photodynamic Inactivation with Exogenous Photosensitizer Curcuma longa Extract Activated by Laser Diode 403 nm on Staphylococcus aureus**
Suryani Dyah Astuti, Amiliyatul Mawaddah, Aulia Mt Nasution, Amalia F Mahmud, Nurul Fitriyah, Idha Kusumawati, Abdurachman, Putri S. Puspita, and Suhariningsih
Pages 155-161

CLINICAL ARTICLE

29. **Analysis of Accessory Canals as Important Anatomical Structures in the Anterior Maxilla with Cone Beam Computed Tomography**
Zurab Khabadze, Ferdaus Taraki, Oleg Mordanov, Saida Abdulkerimova, Yusup Bakaev, Mariam Shubitidze, Shamil Solimanov, Shamil Nazhmudinov
Pages 162-165

JIDMR
JOURNAL OF INTERNATIONAL DENTAL AND MEDICAL RESEARCH

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2020; 13 (1)

CLINICAL ARTICLE

30. **Comparison of educational methods between using leaflets and audiovisuals in order to increase knowledge on the oral cancer among high school students in Jatinangor, West Java, Indonesia**
Winny Yohana, Astsania Hikmah Alfath, Sri Susilawati,Riana Wardani
Pages 166-169

CLINICAL ARTICLE

31. **Effects of Impacted Lower third Molar Removal on Alveolar Bone Height and Periodontal Parameters on Adjacent Second Molar**
Wan Nur Alwani Wan Abdul Aziz, Azlan Jaafar, Ahmad Dzulfikar Samsudin
Pages 170-174

CLINICAL ARTICLE

32. **Description of Salivary Secretion and Number of Facultative Anaerobic Bacterial Colony in Female Smokers**
Yuyun Qurrota A Yunina Rahmi, Sri Tjahajawati, Hening Tjaturina Pramesti
Pages 175-179

CLINICAL ARTICLE

33. **Immunohistochemical Evaluation of Bcl-2 in Mucoepidermoid Carcinoma and Adenoid Cystic Carcinoma of Salivary Glands**
Mustafa Mohammed Abdulhussain, Ali Sami Mohsen
Pages 180-187

CLINICAL ARTICLE

34. **Analysis of Beta-Crosslaps (B-Ctx) and Mandible Trabecular Parameters in Menopausal Women Using Cone Beam Computed Tomography (Cbct)**
Silviana Farrah Diba, Azhari, Farina Pramanik, Sri Tjahajawati
Pages 189-193

CLINICAL ARTICLE

35. **Pattern of Mandibular Third Molar Impaction in Malaysia Population and Their Association with Gender, Age and Race**
Mohammad Subhi Shareif, Sharon Paul, Nurul Fatihah Che Ghani, Ismail Muhamad Fareez
Pages 194-200

CLINICAL ARTICLE

36. **Cytogenetic Profile and Main Comorbidities of School-Aged Children and Adolescents with Down Syndrome in the Northwestern Algeria**
Houari Hamdaoui, Amaria Aouar, Djamel Belkhatir, Abdellatif Moussouni, Zakarya Moqaddem, Sarra Khater
Pages 201-208

CLINICAL ARTICLE

37. **Dental Students Perception Towards Changes Implemented in Clinical Teaching Strategies of Conservative Dentistry and Endodontics**
Mohammad M. Hammad, Mariam M. Al-Abdallah, Ahmad M. El-Ma'aita, Susan N. Hattar
Pages 209-215

CLINICAL ARTICLE

38. **Interdisciplinary Collaboration: Screening of Systemic Blood Flow at a Dental Appointment \ Russia**
Victoriya N. Naumova, Dmitriy V. Mikhalchenko, Julia A. Makedonova, Tatyana V. Kolesova, Larisa N. Denisenko
Pages 216-222

JIDMR
JOURNAL OF INTERNATIONAL DENTAL AND MEDICAL RESEARCH

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2020; 13 (1)

CLINICAL ARTICLE

39. **Correspondence between Dental and Skeletal Maturity Parameters Among Patients with Different Sagittal Relationships at the end of Puberty Period**
Myroslav Goncharuk-Khomyn, Ebru Akleyin, Igor Zhulkevych, Yaroslav Nahirnyi, Pavlo Brekhlichuk, Yuriy Mochalov, Ivan Melnychuk, Liudmyla Horzov, Olesia Stoika
Pages 223-228

CLINICAL ARTICLE

40. **The relationship between sex and age on dental arch change in the reverse twin block appliance on dental study model measurements: A randomized clinical trial**
Osama Bahaa Albajalan, Nawres Oraibi Alazzawi, Nor Ashikeen Mukti, A.R. Samsudin
Pages 229-235

CLINICAL ARTICLE

41. **Comparison the Cost-Effectiveness of Reducing Dentin Hypersensitivity Between Brushing and Massage with Desensitizing Toothpaste Method and Dentinal Tubule Sealant Application Method**
Ronnayut Chansamat, Rutchanoo Chansamart, Patcharaphol Samnieng
Pages 236-240

CLINICAL ARTICLE

42. **Anesthetic efficacy of three different Volumes of 4% Articaine for extraction of maxillary posterior teeth – A randomized trial**
Mahmoud Shalash, Noha M. El Adl, Aalaa S. Emara
Pages 241-245

CLINICAL ARTICLE

43. **Evaluation of the Use of Platelet-Rich Fibrin in Socket Preservation in Patients with Chronic Periodontitis**
Iyad Alsayed, Ali Abousulaiman, Mohammed Monzer Alsabbagh
Pages 246-251

CLINICAL ARTICLE

44. **Oral Health Related Quality of Life Among Adults Attending Periodontal Clinic at Lium Kuantan**
Juzaily Husain, Farah Natashah Mohd, Abdul Hadi Said, Munirah Yaacob
Pages 252-257

CLINICAL ARTICLE

45. **A Study of Information and Communication Technology Competencies for Learning of Dental Students at Naresuan University, Thailand**
Tipruthai Prayoonwong, Nattan krodkaew, Phachara Siripraphonroj, Sirikorn Saedan, Hatayrat Meejitr
Pages 258-269

CLINICAL ARTICLE

46. **Children's Birth Weight and Their Current Body Mass Index in Relation to Early Childhood Caries**
Nor Azwani Mohd Shukri, Nazalikha Lokman, Norashikin Mustafa, Roszanadia Rusali, Nor Asilah Harun
Pages 270-274

CLINICAL ARTICLE

47. **Peri-Implant Marginal Bone Changes and Soft Tissue Conditions Around Single Implants with Laser-Microgrooved Collar Placed in Regenerated Extraction Sockets and in Native Bone: 2-Year Results of RCT**
Guarnieri Renzo, Dario Di Nardo, Maurilio D'Angelo, Marco Seracchiani, Gabriele Miccoli, Luca Testarelli
Pages 275-282

JIDMR
JOURNAL OF INTERNATIONAL DENTAL AND MEDICAL RESEARCH

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2020; 13 (1)

CLINICAL ARTICLE

48. **Clinical Resolution of Periodontitis Among Diabetic Patients under Medical-Dental Coordinated Care: A Preliminary Study in Kuantan**
Munirah Yaacob,Tin Myo Han, Razida Ismail, Sorayah Sidek,Padmini Hari, Mohd Aznan Md Aris, Iskandar Firzada Osman, Mahendran Thuraiappah, Fa'iza Abdulla, Than Tun Sein, Roslan Bin Saub
Pages 283-289

CLINICAL ARTICLE

49. **A Retrospective Evaluation of Requirements and Causes of Dental General Anesthesia in Pediatric Dentistry**
Ahmet Aras, M. Sinan Dogan
Pages 290-294

CLINICAL ARTICLE

50. **Prevalence of Root Caries among Patients Attending RAKCODS Hospital**
Md Sofiqul Islam, Hiba JI Abu Jarad, Dhabyeh alshehhi, Mohannad Nassar, Smriti Aryal AC, Muhammed Mustahsen Rahman
Pages 295-300

CLINICAL ARTICLE

51. **Evaluation of Selection Criteria for Patients Indicated for Fixed Orthodontic Appliance Treatment**
Ammar S. Kadhum, Dheaa H. Al-Groosh, Dhiaa J. Aldabagh, Akram F. Alhuwaizi
Pages 301-305

CLINICAL ARTICLE

52. **Perceived Sources of Stress and Stress Coping Strategies among Junior Dental Students at Ajman University**
Sundus A. A. Al Omar, Al-Moutassem Billah Khair, Nisha Shantakumari, Mawada Abdelmagied, Karrar M. H. Hadi
Pages 306-314

CLINICAL ARTICLE

53. **Effect of obesity on the levels of salivary matrix metalloproteinase-8 (MMP-8) In chronic periodontitis patients**
Usman Rashid, Siti Lailatul Akmar Zainuddin, Zurairah Berahim, Ahmad Azlina, Basaruddin Ahmad, Haslina Taib
Pages 315-320

CLINICAL ARTICLE

54. **Efficiency of BTX-A in the Alleviation of Hemifacial Pain**
Mohammed Rhael Ali, Elham Hazeim Abdulkareem
Pages 321-326

CLINICAL ARTICLE

55. **The Relationship between the Salivary pH, Flow Rate, and the Number of Oral Streptococci in Elementary School Age Children**
Dudi Aripin, Anne Agustina Suwargiani, Riana Wardani, Sri Susilawati, Tadeus Arufan Jasrin, Warta Dewi, Inne Suherna Sasmita
Pages 327-331

CLINICAL ARTICLE

56. **The Effectiveness of Reducing Dentin Hypersensitivity Between Brushing and Massage with Desensitizing Toothpaste Method and Dentinal Tubule Sealant Application Method**
Ronnayut Chansamat, Rutchanoo Chansamart, Patcharaphol Samnieng
Pages 332-336

JIDMR
JOURNAL OF INTERNATIONAL DENTAL AND MEDICAL RESEARCH

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2020; 13 (1)

CLINICAL ARTICLE

57. **Effectiveness of An Educational Workshop in Improving Knowledge on Dental Trauma among Rugby Players**
Amy Kia Cheen Liew, Dalia Abdullah, Mohamad Aflah Lokeman, Muhammad Azril Fitri Kamaruddin, Muhammad Khiratti Mat Zainal, Eason Soo
Pages 337-345

CLINICAL ARTICLE

58. **The Relationship between Oral Health Attitude (HU-DBI) Score and Caries Experience (DMFT) Score among First Year Dental Students in USIM, Malaysia.**
Nazirah Ab Mumin, Haslinda Ramli, Syatirah Najmi Abdullah, Asfizahrasby Mohd. Rasoul, Azlan Jaafar, Haslina Rani
Pages 346-350

CASE REPORT

59. **Effect of Periodontal Treatment of Patient with Orthodontic Fix Appliance- long Term Follow-up, Case Report**
Zana Sllamniku-Dalipi, Fatmir Dragidella, Shefqet Mrasori, Metush Disha, Kastriot Meqa, Visar Bunjaku
Pages 351-354

CASE REPORT

60. **Endodontic Management of Mandibular First Molar with Radix Entomolaris and Weine Type II Root Configuration: A Case Report**
Bernard Iskandar, Dwi Nugroho Juanda
Pages 355-358

REVİEW

61. **Physical and Chemical Conditions for the Long-Term Functioning of Restorations with a Zirconia Framework**
Zurab Khabadze, Oleg Mordanov, Georgy Davreshyan, Anzhela Adzhieva, Omargadzhi Magomedov, Shamil Solimanov, Shamil Nazhmudinov
Pages 359-363

REVİEW

62. **DEF6 Expression and Regulation in Cancer, Chronic Inflammatory Diseases and Autoimmune Diseases: A Review**
Nyi Mas Siti Purwaningsih, Khor Goot Heah, Hong-Jian Zhu, Mazuan N.M. Rosdy, Effat Omar
Pages 364-371

REVİEW

63. **Chemical Oral Health care and Aspiration Pneumonia (AP) in Elderly Patients: A Systematic Literature Review**
Nilobon Aiemyen, Thanida Pothidee, Praweena Sopapornamorn, Pastraporn Payukaparp, Chaipat Luangnam, Songsak Suksan, Pichit Preechasummakul, Patcharaphol Samnieng
Pages 372-378

REVİEW

64. **In Vitro and In Vivo Studies of Ganoderma lucidum in Cancer**
Khor Goot Heah, Syairah Nabila Bt Suhaimi, Nur Rawaidah Bt Mohd Shobri, Hong-Jian Zhu, GRA Froemming
Pages 379-383

REVİEW

65. **Oral Dryness of Elderly Patients with Dementia**
Pattara Sukhumanphaibun, Supaporn Sangouam
Pages 384-387

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2020; 13 (1)

MEDICINE

EXPERIMENTAL ARTICLE

66. Serotyping of Helicobacter Pylori Antibody Reflected on Human Health
Valon Morina, Rrahman Ferizi, Fatmir Cakaj, Mohamed Fawzy Ramadan
Pages 388-394

CLINICAL ARTICLE

67. Risk Factors as an Indicator of Non-Complications Spontaneous Preterm Birth: a Study in Eight Hospitals
Sriyana Herman, Budi Santoso, Hermanto Tri Djoewono, Agus Sulistyono, Hari Basuki, Muhammad Miftahussurur
Pages 395-399

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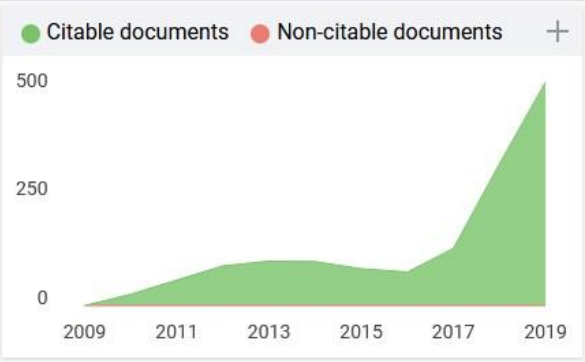
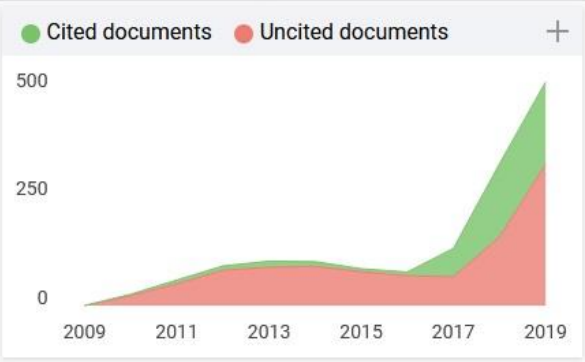
Search





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Zinc Supplementation in Cytokine Regulation During LPS-induced Sepsis in Rodent

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Abstract

Severe sepsis increased pro-inflammatory cytokines and low Zinc levels were also found in patients with sepsis.To explain the mechanisms of sepsis improvement after Zinc administration through cytokine regulations

Total sample of 40 rodents was randomized into 4 groups with treatment of LPS in LPS group and LPS-Zinc and placebo in Control and Zinc group, then followed by blood sampling at the second hour to measure Zinc level by AAS. Furthermore, in the LPS-Zinc and Zinc group, Zinc was administered orally, while the control and LPS group were given placebo orally. The blood samples were then collected at the 8th, 24th, and 72nd hour to measure TNF-α, IL-6, IL-10, and TGF-β by sandwich-ELISA method and the Zinc content was also measured at the 72nd hour using AAS. One-way Anova, Kruskall Wallis, Mann-Whitney, paired t-tests, and Wilcoxon Signed Rank Test were employed as statistical analyses.

There were some decreases in the level of TNF-α and IL-6 plasma and an elevated levels of IL-10 and TGF-β in the LPS-Zinc group compared to the LPS group.

Administration of Zinc in sepsis improve sepsis condition through decreased pro-inflammatory cytokines (TNF-α and IL-6) and increased anti-inflammatory cytokines (IL-10 and TGF-β).

Experimental article (J Int Dent Med Res 2020; 13(1): 46-50)

Keywords: Zinc, sepsis, cytokine

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Introduction

Sepsis remains a world health problem due to its high mortality rate despite optimal therapy using antibiotics, fluids, and inotropes.[1,2] Mortality rate of sepsis in hospitals is approximately 15% among adults and 25% among children.[1,3] During sepsis, an increase in pro-inflammatory cytokines of IL-1β, IL-6, IL-8, IL-12, IFN, and TNF-α are associated with mortality in sepsis.[4] Low serum Zinc levels are also found in severe and critical sepsis among children and adults.[5–7] Zinc supplementation can reduce pro-inflammatory cytokines of IL-6, IL-8, and TNF-α.[5,8,9] In addition, during Zinc deficiency, there is also a low level of anti-inflammatory cytokines of I-4, IL-10 and TGF-β.[10] Several studies have shown that administration of Zinc for sepsis can be useful to reduce mortality rate.[11,12] This study aims to investigate the effect of Zinc on cytokine regulation under septic conditions.

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Materials and methods

Animal studies

This study used a sample of 40 Spraque-Dawley rodents (10-12 weeks old) which were acclimated 2 weeks before treatment, given standard food, and grouped randomly into Control, LPS, LPS-Zinc, and Zinc groups (10 rodents in each group).The administration of LPS *E coli* serotype O111: B4 from Sigma with a dose of 10 mg / kg (500 mg was prepared, yet only 100 mg was taken). Then it was diluted with 10 mL of aquabidest and injected intravenously in the tail of rodents in LPS group and LPS-Zinc group as much as 0.2 mL, whereas in the Control and Zinc groups, rodents were given normal saline of 0.2 mL intravenously. In addition, in order to facilitate intravenous injection, 0.1 mL of ketamine was administered.

Zinc drop (10 mg/mL) (Zincpro® drop 15 mL, Combiphar Indonesia) was diluted to 1 mg/mL Zinc sulfate solution by adding 9 mL of aquabidest to every 1 mL Zinc drop. Two mg/kg of Zinc dose was to human body, or equivalent to 4.65 mg / kg of rodents' body weight. It was given to rodents via gastric tube to the LPS-Zinc and Zinc group with a dose of 1 mL for 3 days, while in the control and LPS groups, rodents were given a placebo aquabidest of 1 mL.

Blood sampling was conducted through rodents' tail for 5 rodents in each group at the second hour to analyze Zinc levels and at the 8th and 24th hours for the next 5 rodents in each group. Then at the 72nd hour, we took blood from rodents' heart and aorta to analyze cytokines of TNF-α, IL6, IL10, and TGF-β. Examination of Zinc levels was also carried out at the 72nd hour. Blood samples without EDTA were centrifuged at 6,000 G for 10 minutes and at 25 ^{o}C within 30 minutes, and then stored in a refrigerator at -20 ^{o}C until they were analyzed.

Plasma Zinc

Plasma Zinc was assayed by Atomic Absorption Spectrophotometry (AAS) methods that was used in the laboratory of Science and Technology, Brawijaya University. This methods had been described in the previous study (13).

Cytokine analysis

Measurements of cytokines. The concentrations of TNF-α, IL6, IL10, and TGF-β in the supernatant were measured by sandwich-ELISA, using a FineTest ELISA Kit manual instruction's from Wuhan Fine Biological Technology Co.,Ltd. This study was approved by the Ethical Commitee of the Brawijaya University Malang.

Statistical analysis

The data are expressed as means ± SDs. All data in 4 groups were compared using one-way Anova and post hoc test. If the data were not normally distributed, further Kruskal-Wallis test was employed. The data in a group at the 8th, 24th, and 72nd hour were compared with same subject anova when the data distribution was normal, or Friedman anova if they were not normally distributed. The data of Zinc level at the 2nd and 72nd hours were analyzed with t-test dependent.

Results

During study, two rodents were dead in LPS group at the 8th and 24th hour. In this study the minimal sample for each group was 5 and duplicated to 10, because there was blood collection more than 2 times in 24 hours. Sample characteristics between groups were comparable, as depicted in Table 1 which shows that there is no differences in rodents' weight in 4 groups.

Body weight (g)						
Group	**n**	**Mean**	**SD**	**Minimum**	**Maximum**	**p**
Control	5	221.40	6.50	213	229	0.34
LPS	5	240.80	10.50	225	253	
LPS-Zinc	5	226.60	19.46	208	256	
Zinc	5	232.80	24.81	201	263	

Table 1. Rodents' body weights in 4 groups

LPS E Coli administration influences plasma Zinc level

The effects of intravenous LPS *E Coli* on Zinc levels are illustrated in Table 2. Giving intravenous LPS *E Coli* to the LPS and LPS-Zinc groups can reduce Zinc levels below normal levels with normal values of Zinc levels 0.84-1.59 mg / L, though there are no differences between the four groups. Increased Zinc levels were found in the LPS, LPS-Zinc, and Zinc groups at the 72nd hour. The increase Zinc levels in the LPS and LPS-Zinc groups illustrated some fluctuations in Zinc levels during sepsis condition. While for the case of Zinc group, it proved that giving Zinc supplementation for 3 days could increase Zinc levels. Zinc levels at the 72nd hour of the control group, LPS, and LPS-Zinc were not significantly different, which showed fluctuations in Zinc levels during sepsis.

Plasma Zinc (mg/L)				
Group	**n**	**2 hours**	**72 hours**	**p**
Control	5	0.87 ± 0.09 (0.75-0.97)	0.91 ± 0.22^{a} (0.57-1.19)	0.67
LPS	5	0.62 ± 0.21 (0.42-0.97)	1.14 ± 0.24^{a} (0.94-1.54)	0.04†
LPS-Zinc	5	0.75 ± 0.06 (0.71-0.86)	0.99 ± 0.07^{a} (0.94-1.11)	0.04†
Zinc	5	0.87 ± 0.18 (0.62-1.12)	1.49 ± 0.17^{b} (1.33-1.74)	0.001†
p		0.07	0.001*	

Table 2. Plasma Zinc at the 2nd and 72nd hour after LPS E coli administration.

* Significant at α=0.05 (One way Anova)
† Significant at α=0.05 (Paired t-test / Wilcoxon Signed Rank Test)
[a,b] Same superscript in the column revealed no difference between groups (multiple comparisons LSD)

Zinc supplementation reduces the pro-inflammatory cytokine

Modeling of sepsis experimental animals in this study using intravenous injection of LPS *E coli* was successful, which was characterized by an inflammatory response in the form of high levels of pro-inflammatory cytokines of TNF-α and IL-6 in the LPS and LPS-Zinc groups compared to the control group. Zinc supplementation reduced levels of pro-inflammatory cytokines of TNF-α and IL-6 in septic experimental animals, which was seen from the lower levels of pro-inflammatory cytokines in the LPS-Zinc group compared to LPS at the 8th, 24th, and 72nd hour. TNF cytokine values -α of the LPS group fluctuated at 8th, 24th, and 72nd hour. Similar occurrence also happened in the control group.While the cytokine values of IL-6 in LPS and LPS-Zinc groups fluctuated at the 8th, 24th, and 72nd hour, peaking at the 24th hour and sloping down at the 72nd hour. These results are illustrated in Tables 3 and 4.

TNF-α plasma concentration (pg/mL)

Group	n	8th hour	24th hour	72nd hour	p
Control	5	79.95 ± 2.04[a] (76.55-81.55)	81.55 ± 1.30[a] (80.55-84.05)	76.35 ± 3.19[a] (71.55-80.55)	0.029†
LPS	5	122.55 ± 11.40[c] (111.55-136.55)	110.05 ± 5.48[c] (106.55-119.05)	108.05 ± 4.87[d] (101.55-114.05)	0.034†
LPS-Zinc	5	92.75 ± 1.25[b] (91.55-94.55)	95.35 ± 2.17[b] (91.55-96.55)	93.35 ± 2.49[c] (91.55-96.55)	0.211
Zinc	5	77.85 ± 4.15[a] (71.55-81.55)	76.55 ± 6.12[a] (71.55-86.55)	82.35 ± 4.27[b] (76.55-86.55)	0.101
p		0.000*	0.001*	0.001*	

Table 3. TNF-α plasma concentration at 8th, 24th, and 72nd hours.
* Significant at α=0.05 (Brown-Forsythe/Kruskal-Wallis)
† Significant at α=0.05 (Same subject Anova/Anova Friedman)
[a,b,c,d] Same superscript in the column revealed no difference between groups (*multiple comparisons* Games-Howell/Mann-Whitney)

IL-6 plasma concentration (pg/mL)

Group	n	8th hour	24th hour	72nd hour	p
Control	5	1.58 ± 0.09[a] (1.42-1.64)	1.39 ± 0.11[a] (1.31-1.55)	1.57 ± 0.05[a] (1.53-1.63)	0.091
LPS	5	4,91 ± 0,40[c] (4.25-5.21)	5.57 ± 0.16[d] (5.54-5.93)	3.39 ± 0.38[c] (3.09-4.05)	0.000†
LPS-Zinc	5	2.15 ± 0.09[b] (2.06-2.25)	3.83 ± 0.19[c] (3.64-4.11)	2.51 ± 0.15[b] (2.34-2.74)	0.000†
Zinc	5	2.10 ± 0.17[b] (1.91-2.27)	2.21 ± 0.44[b] (1.81-2.72)	1.84 ± 0.26[a] (1.55-2.14)	0.304
p		0.000*	0.000*	0.001*	

Table 4. IL-6 plasma concentration at the 8th, 24th, and 72nd hour.

*Significant at α=0.05 (Brown-Forsythe/Kruskal-Wallis)
† Significant at α=0.05 (Same subject Anova)
[a,b,c,d] Same superscript in the column revealed no difference between groups (multiple comparisons Games-Howell/Mann-Whitney)

Zinc supplementation increases anti-inflammatory cytokine

In contrast to pro-inflammatory cytokines, Zinc increases anti-inflammatory cytokines of IL-10 and TGFβ. There were higher levels of IL-10 and TGF-β in the LPS-Zinc group than in the LPS group at the 8th, 24th, and 72nd hour. The IL-10 levels of LPS and LPS-Zinc groups fluctuated at the highest levels at the 24th hour. TGF-β level of the LPS group was also fluctuated with the same pattern, while the TGF-β level of the LPS-Zinc group found a different pattern, namely there was a gradual increase from the 8th to the 72nd hour.

IL-10 plasma concentration (pg/mL)

Group	n	8th hour	24th hour	72nd hour	p
Control	5	1.27 ± 0.04[a] (1.24-1.34)	1.37 ± 0.08[a] (1.31-1.46)	1.38 ± 0.05[a] (1.33-1.44)	0.07
LPS	5	2.12 ± 0.21[b] (1.83-2.33)	3.83 ± 0.32[c] (3.37-4.11)	2.17 ± 020[c] (1.95-2.48)	0.000†
LPS-Zinc	5	2.96 ± 0.52[b] (2.38-3.78)	5.16 ± 0.56[d] (4.52-5.74)	4.06 ± 0.57[d] (3.26-4.51)	0.002†
Zinc	5	2.11 ± 0.29[b] (1.85-2.54)	1.99 ± 0.39[b] (1.65-2.64)	1.63 ± 0.14[b] (1.51-1.87)	0.06
p		0.000*	0.000*	0.000*	

Table 5. IL-10 plasma concentration at 8th, 24th, and 72nd hours
* Significant at α=0.05 (Brown-Forsythe/Kruskal-Wallis)
† Significant at α=0.05 (Same subject Anova)
[a,b,c,d] Same superscript in the column revealed no difference between groups (*multiple comparisons* Games-Howell/Mann-Whitney)

TGF-β plasma concentration (pg/mL)

Group	n	8th hour	24th hour	72nd hour	p
Control	5	0.80 ± 0.03[a] (0.76-0.84)	0.85 ± 0.06[a] (0.76-0.92)	0.77 ± 0.03[a] (0.74-0.83)	0.08
LPS	5	1.75 ± 0.09[b] (1.64-1.87)	2.02 ± 0.38[c] (1.68-2.59)	1.98 ± 0.29[c] (1.60-2.39)	0.35
LPS-Zinc	5	2.59 ± 0.24[c] (2,37-2.97)	3.95 ± 0.27[d] (3.73-4.42)	4.74 ± 0.25[d] (4.40-4.98)	0.000†
Zinc	5	1.73 ± 0,17[b] (1.57-1.97)	1.65 ± 0.20[b] (1.48-1.90)	1.37 ± 0.16[b] (1.21-1.55)	0.05
p		0.000*	0.000*	0.000*	

Table 6. TGF-β plasma concentration at the 8th, 24th, and 72nd hour
* Significant at α=0.05 (Brown-Forsythe/Oneway Anova)
† Significant at α=0.05 (Same subject Anova)
[a,b,c,d] Same superscript in yhr column revealed no difference between groups (*multiple comparisons* Games-Howell/LSD)

Discussion

This study showed some improvements in sepsis in terms of decreased inflammatory response in the form of decreasing pro-inflammatory cytokines (IL-6 and TNF-α) and increasing anti-inflammatory cytokines (IL-10 and TGF-β). This study is different from previous studies for rodent which were given Zinc before being induced to sepsis by CLP. In the previous study, similar results were obtained in the form of a decrease in pro-inflammatory cytokines of IL-6 and IL-1β.[14] In this study, sepsis was modeled in experimental animals by administering intravenous LPS *E. Coli.* The use of intra-venous LPS *E Coli* as a sepsis experiment in animal model was similarly used in previous studies, resulting in the increase of pro-inflammatory cytokines.[15,16] The successful use of LPS *E coli* for the inflammatory reaction caused by sepsis in animal models in this study was demonstrated by an increase in pro-inflammatory cytokines (TNF-α and IL-6) and anti-inflammatory cytokines (IL-10 and TGF-β). An increase in pro-inflammatory cytokines (TNF-α and IL-6) and anti-inflammatory cytokines (IL-10 and TGF-β) are associated with the worsening or progression of sepsis.[17] Increasing pro-inflammatory cytokine TNF-α and IL-6 are also occured in local infection such as periodontitis.[18]

The decrease in plasma Zinc level in two hours after the administration of LPS *E coli* in the LPS and LPS-Zinc groups in this study was not as large as the decrease in plasma Zinc levels in sepsis and critical conditions in the previous study (45-48 µg / dL).[5–7] In this study, the mean Zinc level in the LPS group was 0.62 mg/L or 62 µg /dL and the mean LPS-Zinc group's Zinc level was 0.75 mg /L or 75 µg/dL which was included in Zinc deficiency criteria according to the normal Zinc levels of 84 - 159 µg / dL.[18] While in the control and Zinc groups, there were normal Zinc levels, though there were no differences with the LPS and LPS-Zinc groups. For this study, symptoms of sepsis might be triggered by intravenous LPS *E coli* and did not cause severe sepsis symptoms. Low Zinc levels in sepsis, which were found in patients with severe and critical sepsis in children and adults, were associated with mortality.[5–7] Blood's low Zinc levels in sepsis are caused by the influence of pro-inflammatory cytokines (namely IL1β and IL-6) which activate STAT mediated signals and upregulation of ZIP14 and ZIP 6; then, they also trigger intracellular blood Zinc influx (20). Low Zinc levels and increase in cytokines of IL-6, IL-8, IL-1 TN, and TNF-α occur more frequently in sepsis, compared to healthy individuals.[5]

Increased levels of TNF-α are found in sepsis and associated with shock, coagulopathy, death, and survival. TNF-α is also used as a sepsis diagnosis and evaluation of therapy in sepsis.[20] TNF-α has an important role in inflammation. Moreover, rhTNF's administration in experimental animals can cause symptoms of hypotension, metabolic acidosis, massive pulmonary hemorrhage, acute tubular necrosis in kidney, and gastrointestinal bleeding lesions.[21,22] TNF-α levels in experimental animals injected with LPS *E coli* and oral Zinc administration was lower than the experimental group injected with LPS *E coli* and given placebo in this study. The decrease in TNF-α in the group given Zinc was also found in previous studies, such as in cases of diarrhea in children,[23] sepsis in rodents as animal model,[9] sickle-cell disease,[24] and incidence of infection among elderly.[25]

Increase in IL-6 occurs in SIRS conditions associated with infection and mortality.[26,27] Increase in IL-6 in severe sepsis causes an increase in capillary leak and a decrease in intestinal contractions.[28,29] The administration of Zinc in this study reduced IL-6 level in experimental animal groups which were injected with intravenous LPS *E coli* and Zinc, compared to the experimental group which was only injected with LPS *E coli*.

IL-10 and TGF-β are anti-inflammatory cytokines secreted by Treg. Previous study showed that giving Zinc to healthy people for 10 days can induce Treg.[30] IL-10, which was secreted by Treg, inhibits Th1, so pro-inflammatory cytokines from Th1 are reduced.[31] In this study, an increase in IL-10 in the LPS-Zinc group was higher than the LPS group. It indicated that Zinc's effect on the increase in IL-10 cytokines already occurred at the 8th hour. In the previous study, there was an increase after 10 days of Zinc administration, because no analysis was performed at an earlier hour.[30] Increased TGF-β secretion, which is an anti-inflammatory cytokine secreted by Treg, occurs in the LPS-Zinc group compared to the LPS group. Giving Zinc can increase TGF-β1, elevation of intestinal villi, and ratio villi crypt in the intestine, so that it can improve intestinal

permeability.[32] TGF-β can inhibit TNF-α cytokines through translated inhibition of TNF mRNA.[33]

The typical decreased vertical facial height of this patient resulted from the congenital.

Conclusions

Administration of Zinc in sepsis can improve sepsis condition through cytokine regulation in the form of decreased pro-inflammatory cytokines (TNF-α and IL-6) and increased anti-inflammatory cytokines (IL-10 and TGF-β).

Declaration of Interest

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