Volume 2, Issue 1, June 2022 - ISSN 2812-4898

مركز الأكاديمية للنشر
ACADEMY Publishing Center

AMPDR

Advances in Medical, Pharmaceutical and Dental Research Journal

Academy Publishing Center
Advances in Medical, Pharmaceutical and Dental Research [AMPDR]
First edition 2021

ACADEMY Publishing Center

AMPDR

Volume 2, Issue 1, [June 2022]

eISSN: 2812-4898

pISSN: 2812-488X

Arab Academy for Science, Technology, and Maritime Transport, AASTMT Abu Kir Campus, Alexandria, EGYPT
P.O. Box: Miami 1029
Tel: [+203] 5622366/88 – EXT 1069 and [+203] 5611818
Fax: [+203] 5611818
Web Site:http://apc.aast.edu

Advances in Medical, Pharmaceutical and Dental Research is a peer-reviewed, open access, multidisciplinary journal with two issues yearly. The aim of the journal is to publish updated reviews besides research articles with comprehensive theoretical and experimental details. Short communications are also accepted. The multidisciplinary journal welcomes manuscripts covering a wide range of aspects involved in medical, pharmaceutical and dental sciences. All submitted articles should report original, previously unpublished research results, experimental or theoretical. Articles submitted to the journal should meet these criteria and must not be under consideration for publication elsewhere. The manuscript should follow the style specified by the journal.

The journal is open-access with a liberal Creative Commons Attribution-NonCommercial 4.0 International License which preserves the copyrights of published materials to the authors and protects it from unauthorized commercial use.

The AMPDR journal does not collect Articles Processing Charges [APCs] or submission fees, and is free of charge for authors and readers, and operates an online submission with the peer review system allowing authors to submit articles online and track their progress via its web interface.
The journal is financially supported by the Arab Academy for Science, Technology, and Maritime Transport AASTMT in order to maintain quality open-access source of research papers.

AMPDR has an outstanding editorial and advisory board of eminent scientists, researchers and engineers who contribute and enrich the journal with their vast experience in different fields of interest to the journal.

Editorial Committee

Associate Editors

Editorial Board

Administrative Committee

Table of Contents

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.001

June 2022
Volume 2
Issue 1

Updated mini-review of the chemistry, pharmacology and validated assays for U.S. FDA approved COVID-19 therapeutic agents

Miranda F. Kamal[1*], Mohamed S. Nasr[1], Yousef S. Elshamy[2], Nehal W. El Sayed[3] and Sara M Mohyeldin[1]

[1]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Damanhour University, Beheira, Egypt.
[2]Department of Chemistry, C. Eugene Bennett, West Virginia University, Morgantown, WV, 26506, USA.
[3]Department of Pharmaceutical Analytical Chemistry, College of Pharmacy, Arab Academy for Science, Technology and Maritime Transport, Egypt.

Email: mirandafawzy@yahoo.com, mohamed.nasr@pharm.dmu.edu.eg, dr.joealshamy@yahoo.com, nehal.w.saad@gmail.com, sara_mo7ydeldin@hotmail.com

Received on, 26 February 2022 - Accepted on, 22 May 2022 - Published on, 17 June 2022

Abstract:

The fish market in Wuhan, China was the epicenter of Covid-19 pandemic, brought about by the SARS-CoV-2 virus, resulting in significant economic and social worldwide disruption. Although numerous drugs have been indicated for treating the viral infection and/or its symptoms, the U.S. FDA to date has granted approvals for only four therapeutic agents, namely the small-molecules Remdesivir, Baricitinib and two monoclonal antibody combinations amlanivimab/etesevimab and casirivimab/imdevimab]. This review deals with the chemical and pharmacological aspects of these approved therapeutic agents as well as the properties of their reported marketed formulations and biological matrices. Furthermore, it presents a comparison between the cited analytical methodologies for each drug separately. A comprehensive, detailed, mini-overview of Coronavirus authorized therapeutics is also presented.

Key words: *Covid-19, Remdesivir, Baricitinib, Monoclonal antibodies*

1. INTRODUCTION

Coronaviruses [CoVs], or Coronaviridae, are a family of positively enfolded RNA viruses that can infect birds and mammals. Alpha-, Beta-, Gamma- and Delta-CoVs are all known to infect some mammals including humans. However, many CoV infections cause self-controlled symptoms. Infection in humans by two Beta-CoVs, namely SARS-CoV and MERS-CoV resulted in higher than 10 thousand cases with death rates of 37% and 10% for MERS-CoV and SARS-CoV-2 [or "COVID-19"], respectively [1, 2].

In December 2019, atypical pneumonia cases, caused by the previously-unknown Coronavirus, CoV-2, were detected in China[3]. As at May 13, 2022 more than 517,648,631 confirmed cases of COVID-19, including 6,261,708 deaths have been documented due to the CoV-2 virus and its variants [https://covid19.who.int]. Infection is spread through air, on surfaces and incubates with no obvious symptoms during the first 2–14 days post-exposure [4]. Fever, exhaustion, muscle weakness, difficulty in respiration and dry coughing, are the main characteristics of the infection and CoV-2 leads to acute lung injury [5, 6]. In early 2020, the WHO declared Covid-19 to be a pandemic [7].

CoV-2 possesses four essential structural proteins; envelope [E], membrane [M], nucleocapsid [N], and spike [S] proteins; subsidiary [non-structural] proteins; a papain-like protease and three chymotrypsin proteases. The proteases are responsible for the cleavage of viral polypeptides into functional units; and RNA-dependent RNA polymerase [RdRp] which is essential for replication and transcription of the virus [8]. SARS-CoV-2 penetrates living cell by attaching its S-protein to the ACE-2 receptor [9]. Protein-S, PLpro, 3CLpro, RdRp as well as ACE-2 have been targeted in developing antiviral therapeutics [10].

No specific single treatment has yet been developed to treat COVID-19 cases. Researchers have pointed to many therapeutic viral targets in order to develop highly-efficient, least-toxic medications[11]. Mainly however, dealing with infected patients thus far has relied on managing their symptoms. WHO treatment guidelines stress sufficient balanced nutrition, much rest and hydration, in addition to the use of antibiotics [12]. Furthermore, control and prevention by social distancing and elevating immunity have been applied [13, 14].

This presentation addresses FDA-approved drugs which have been reported as having anti-COVID-19 therapeutic effect. Furthermore, their chemistry is reviewed as well as assay methods which are used for Remdesivir, Baricitinib and monoclonal antibodies in their pharmaceutical forms and biological matrices. The

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.001

literature cited herein summarizes the latest updates and lays groundwork for future proceedings.

2. FDA approved COVID-19 therapeutic agents:

2.1. Remdesivir [REMDS]:

REMDS [Veklury®; GS-5734] is a novel antivirulant which was originally developed by Gilead Sciences for the management of Ebola as well as Marburg viral infections [15]. Remdesivir, 2-ethylbutyl [2S]-2-[[2R,3S,4R,5R]-5-[4-aminopyrrolo [2,1-f] [1,2,4] triazin-7-yl]-5-cyano-3,4-dihydroxyoxolan-2-yl] methoxy-phenoxy phosphoryl] amino] propanoate [Figure 1], is a prodrug of a nucleoside analog that perturbs viral replication. It is an off-white non hygroscopic solid, practically water insoluble, but soluble in ethanol [16].

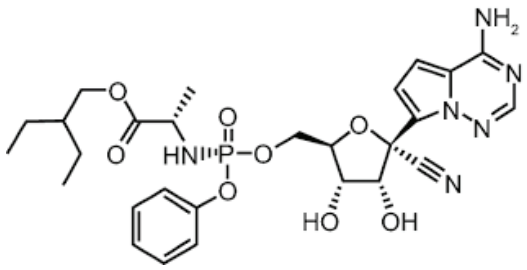


Fig. 1: Chemical structure of REMDS

REMDS is the first and only anti-viral approved by FDA, for hospitalized COVID-19 adults and children over the age of 12 years [weight ≥ 40 kg]. It possesses a complex activation pathway. It metabolizes into [GS-704277] then into [GS 441524], and its major metabolite GS-441524 is instantly changed into the nucleoside triphosphate analog, GS-443902. Overall, it inhibits viral RdRp activity via non-obligate termination of RNA chains, after activation to a triphosphate [17, 18].

The published literature reveals that only LC-MS methods have been applied for REMDS determination in plasma. All of the reported studies focus on the drug's pharmacokinetics and pharmacodynamics. In 2016, Warren et al. [19] developed a LC-MS-MS protocol for a kinetic study of REMDS in uninfected male rhesus monkeys. In 2020, Alvarez et al. [20] determined REMDS and GS-441524 in human plasma using an LC-MS/MS method with the help of a simple protein precipitation [PP] step using a mixture of methanol and zinc sulphate [1.0 M]. A LC-ESI [+]-MS/MS method was also used by Humeniuk et al. [21] to determine plasma REMDS concentrations. Pasupuleti et al.[22] demonstrated a liquid/liquid micro extraction technique coupled with UHPLC/PDA and UHPLC/MS/MS. Recently, Avataneo et al. [23] described UHPLC-ESI[+]-MS/MS, a fast technique [total run time < 2.5 min] to quantify REMDS and GS-441524, in spiked human plasma. The same UPLC system was then employed by Tempestilli et al. [24] for pharmacokinetic evaluation of REMDS and GS 441524 in real patients.

2.2. Baricitinib:

Baricitinib [Olumiant®] is a selective, reversible Janus kinase inhibitor invented by Eli/Lilly Company, originally for treating arthritis and dermatitis[25]. Baricitinib, 2- [1-[ethane sulfonyl]-3-[4-{7H-pyrrolo[2,3-d] pyrimidin-4-yl}-1H-pyrazol-1-yl] azetidin-3-yl] acetonitrile [Figure 2], is an immunomodulatory agent with a significant anti-inflammatory effect [26]. The U.S. FDA has granted EUA for its use simultaneous to REMDS, to treat hospitalized cases [27]. The combination was better than REMDS only in shortening time to recover [28].

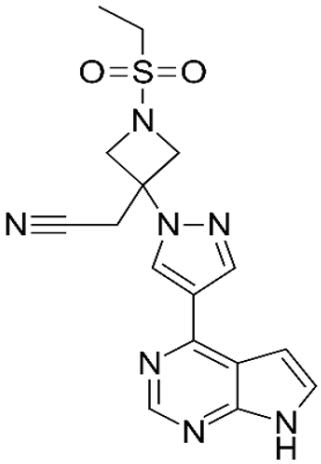


Fig. 2: Chemical structure of Baricitinib

The structure was predicted using artificial intelligence algorithms. Baricitinib inhibits intracellular cytokines that elevate in late cases; including interleukins-2, -6, -10, γ-interferon, and granulocyte macrophage colony-stimulating factor [29-31]. The literature reveals two LC assay methods for its determination in rat plasma, for the drug's pharmacokinetics [32, 33]. The former reported the use of LC/MS/MS for estimation of Baricitinib and Methotrexate [32], whereas the other used UPLC [33]. Recently, a UV-spectroscopic assay was developed for the pure form of the drug and in its dosage form [34]. Furthermore, a RPLC-Diode array detection system was applied for a stability indicating study of Baricitinib [35].

2.3. Monoclonal antibodies:

Monoclonal antibodies are recombinant synthetic proteins that target specific parts of target antigens. They are produced from virus-specific B cells extracted from convalescent plasma or from humanized mice. They show therapeutic efficacy in different viral infections, cancers and different autoimmune diseases [36]. Their antiviral effect is conferred via binding to virus spike proteins thus blocking their binding to ACE2 receptors. This passive immunotherapy is particularly important for outpatient treatment of vulnerable, high-risk individuals or those with mild-moderate infection [37]. As of February 2021, the U.S. FDA has granted Emergency Use Authorization [EUA] for different monoclonal antibodies in COVID-19 treatment. These include combined Bamlanivimab/Etesevimab [38] and combined Casirivimab/Imdevimab [39]. To date, there is no reported methods for analytical quantitation of these monoclonal antibodies.

3. Results and Discussion

Reported Remdesivir assays are limited to biological matrices using a LC-MS technique. Warren et al. [19] determined Remdesivir in the plasma of monkeys with adequate sensitivity, although neither linearity range nor other validation elements were mentioned. Alternatively, Alvarez et al. [20] quantified Remdesivir and its metabolite in human plasma using small plasma volumes and a simple sample preparation procedure. Slightly higher lower limit of quantitation [LLOQ] values were obtained for GS-441524 [5.0 ng/mL]. After the optimization and validation according to European Medicines Agency guidelines, the latter technique was efficiently involved in a kinetic study in a COVID-19 patient after a single dose of Remdesivir [200 mg i.v]. Humeniuk et al.[21] determined REMDS linearly over the range of 4-4,000 ng/mL, and GS-704277 and GS-441524 over 2-2,000 ng/mL.

Pasupuleti et al.[22] monitored the profile of medication in plasma using UPLC/PDA and UPLC/MS/MS in comparison to Avataneo et al. [23] using UPLC-ESI[+]-MS/MS. The latter achieved higher sensitivity for an advanced pharmacokinetic profile during the current worldwide outbreak. The same UHPLC system was then employed by Tempestilli et al. [24] for the pharmacokinetic evaluation of REMDS. Since most studies, including in vivo pharmacokinetics, require a large number of samples to analyze, run time per sample can be very important. The main benefit of reported methodologies is the easy step of preparing the samples, that in turn reduces time of analysis. Although recoveries obtained by LC-MS/MS [20, 21] and UPLC-MS/MS [23, 24] were similar, UHPLC gave significantly better precision.

Both reported LC-MS methods [32, 33] for Baricitinib quantitation were in rat plasma; either in combination with Methotrexate over a concentration range of 0.5–250 ng/mL for both analytes, or as a single component, with 0.2 ng/mL as lower limit of quantitation. A simple spectroscopic A-max method [34] estimated Barictinib over 10-60 µg/mL in laboratory-made tablets. Meanwhile, a reported stability-indicating RP-LC-DAD method [35] was linear at range 10-150µg/mL. No single statement has been reported for simultaneous determination of "Remdesivir and Baricitinib", the FDA approved combination. In the meanwhile, monoclonal antibodies have not been assayed with the aid of analytical techniques.

4. Conclusion:

To sum up, the urgent need for an effective treatment for Covid-19 is of high concern and consideration. However, additional research for possible interactions, and toxicities of the approved medication is complementary for their administration and long-term use.

The present mini-review presents a brief summary of the coronavirus implicated in the SARS-CoV-2 or COVID-19 disease etiology as well as its early onset in China. A short overview is presented of three current FDA approved therapeutics for Covid-19 treatment. The review also summarizes these drugs' different chemical structures, their mechanisms of action and reported assay methods. A comparative summary of reported methods for each drug is separately discussed. This article provides concisely a basic "take-home-message" for the readers seeking information about such an arguing question, "What drugs are being used for Coronavirus SARS-CoV-2??"

5. References

[01] F. Rabi, M. Al Zoubi, G. Kasasbeh, et al., "SARS-CoV-2 and coronavirus disease 2019: What we know so far," Pathogens, vol. 9, issue 3, pp. 231 March,2020.

[02] C. Lai, T. Shih, W. Chien, W. Ko, et al., "Severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] and coronavirus disease-2019 [COVID-19]: The epidemic and the challenges," Int J Antimicrob Agents, vol. 55, issue 3, p. 105924, March, 2020.

[03] "WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020," https://www.who.int/director-general/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 [accessed Feb. 11, 2020]

[04] C. Sohrabi, Z. Alsafi, N. O'Neill, et al., "World Health Organization declares global emergency: A review of the 2019 novel coronavirus [COVID-19]," International journal of surgery, vol. 76, pp. 71-76, April,2020.

[05] [5] Weiskopf, D., K.S. Schmitz, M.P. Raadsen, et al." Phenotype of SARS-CoV-2-specific T-cells in COVID-19 patients with acute respiratory distress syndrome." medRxivZx, vol 5, issue 48, eabd2071, June, 2020.

[06] H. Li, L. Liu, D. Zhang, et al., "SARS-CoV-2 and viral sepsis: observations and hypotheses," Lancet, vol. 395, issue 10235, pp. 1517-1520, May 2020.

[07] J. Sanders, M. Monogue, T. Jodlowski, et al., "Pharmacologic Treatments for Coronavirus Disease 2019 [COVID-19]: A Review," JAMA, vol. 323, issue 18, pp. 1824-1836, April, 2020.

[08] I. Astuti, Ysrafil, "Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2]: An overview of viral structure and host response, " Diabetes Metab Syndr, vol. 14, issue 4, pp. 407-412, July, 2020.

[09] H. Zhang, J. Penninger, Y. Li, et al., "Angiotensin-converting enzyme 2 [ACE2] as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target," Intensive Care Med, vol. 46, issue 4, pp. 586-590, April, 2020.

[10] C. Liu, Q. Zhou, Y. Li, et al., "Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases," ACS Central Science, vol. 6, issue 3, pp. 315-331, March, 2020.

[11] Y. Shi, X. Zhang, K. Mu, et al.," D3Targets-2019-nCoV: a webserver for predicting drug targets and for multi-target and multi-site based virtual screening against COVID-19, "Acta Pharmaceutica Sinica B, vol. 10, issue 7, pp. 1239-1248, July, 2020.

[12] W. Alhazzani, M. Møller, Y. Arabi, et al., "Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 [COVID-19]," Intensive Care Med, vol. 46, issue 5, pp. 854-887, March, 2020.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.001

[13] S. Hamid, M. Mir, G. Rohela, "Novel coronavirus disease [COVID-19]: a pandemic [epidemiology, pathogenesis and potential therapeutics]," New microbes and new infections, vol. 35, pp.100679, April, 2020.

[14] M. Lythgoe, P. Middleton, "Ongoing Clinical Trials for the Management of the COVID-19 Pandemic," Trends Pharmacol Sci, vol. 41, issue 6, pp. 363-382, June, 2020.

[15] R. Eastman, J. Roth, K. Brimacombe, et al., "Remdesivir: A Review of Its discovery and development leading to emergency use authorization for treatment of COVID-19," ACS Central Science, vol. 6, issue 5, pp. 672-683, May, 2020.

[16] DrugBank. [2020, April. 26]. Remdesivir [Online]. Available: https://www.drugbank.ca/drugs/DB14761.

[17] S. Jorgensen, R. Kebriaei, D. Dresser, "Remdesivir: Review of Pharmacology, Pre-clinical Data, and Emerging Clinical Experience for COVID-19." Pharmacotherapy, vol. 40, issue 7, pp. 659-671, July, 2020.

[18] E. Amirian, J. Levy, "Current knowledge about the antivirals remdesivir [GS-5734] and GS-441524 as therapeutic options for coronaviruses," One Health, vol. 9, issue 27, p. 100128, May, 2020.

[19] T. Warren, R. Jordan, M. Lo, et al., "Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys," Nature, vol. 531, issue 7594, pp. 381-385, March , 2016.

[20] J. Alvarez, P. Moine, I. Etting, et al., "Quantification of plasma remdesivir and its metabolite GS-441524 using liquid chromatography coupled to tandem mass spectrometry. Application to a Covid-19 treated patient," Clin Chem Lab Med, vol. 58, issue 9, pp. 1461-1468, June, 2020.

[21] R. Humeniuk, A. Mathias, H. Cao, et al., "Safety, tolerability, and pharmacokinetics of remdesivir, An antiviral for treatment of COVID-19, in healthy subjects," Clinical and Translational Science, vol. 13, issue 5, pp. 896-906, June, 2020.

[22] R. Pasupuleti, P.Tsai, V. Ponnusamy, et al., "Rapid determination of remdesivir [SARS-CoV-2 drug] in human plasma for therapeutic drug monitoring in COVID-19-Patients," Process Biochemistry, vol. 102, issue 18, pp. 150-156, December, 2020.

[23] [23] V. Avataneo, A. de Nicolò, J. Cusato, et al., "Development and validation of a UHPLC-MS/MS method for quantification of the prodrug remdesivir and its metabolite GS-441524: a tool for clinical pharmacokinetics of SARS-CoV-2/COVID-19 and Ebola virus disease," J Antimicrob Chemother, vol. 75, issue 7, pp. 1772-1777, May, 2020.

[24] M. Tempestilli, P. Caputi, V. Avataneo, et al., "Pharmacokinetics of remdesivir and GS-441524 in two critically ill patients who recovered from COVID-19," J Antimicrob Chemother, vol. 75, issue 10, pp. 2977-2980, July, 2020.

[25] P. Taylor, E. Keystone, D. van der Heijde, et al.," Baricitinib versus placebo or adalimumab in rheumatoid arthritis," New England Journal of Medicine, vol. 376 ,issue 7, pp. 652-662, February, 2017.

[26] [26] DrugBank. [2020, April. 30] Baricitinib. [Online]. Available: https://go.drugbank.com/drugs/DB11817

[27] S. Jorgensen, C.Tse, L. Burry, et al., "Baricitinib: a review of pharmacology, safety, and emerging clinical experience in COVID-19," Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, vol. 40, issue 8, pp. 843-856, June, 2020.

[28] Kalil, A.C., T.F. Patterson, A.K. Mehta, et al." Baricitinib plus remdesivir for hospitalized adults with COVID-19," New England Journal of Medicine, vol. 384, issue 9, pp. 795-807, March, 2021.

[29] X. Zhang, Y. Zhang, W. Qiao, et al., "Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19," Int Immunopharmacol, vol. 86, p. 106749, September, 2020.

[30] W. Luo, , Y. Li, L. Jiang, et al., "Targeting JAK-STAT signaling to control cytokine release syndrome in COVID-19," Trends in pharmacological sciences, vol. 41, issue 8, pp. 531-543, August, 2020.

[31] T. Hoang, M. Pino, A. Boddapati, et al., "Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques," Cell, vol. 184, issue 2, pp. 460-475, January, 2021.

[32] S. Veeraraghavan, S. Thappali, S. Viswanadha, et al., "Simultaneous Quantification of Baricitinib and Methotrexate in Rat Plasma by LC-MS/MS: Application to a Pharmacokinetic Study," Sci Pharm, vol. 84, issue 2, pp. 347-359, April-June, 2016.

[33] E. Ezzeldin, M. Iqbal, Y. Asiri, et al., "A Hydrophilic interaction liquid chromatography-tandem mass spectrometry quantitative method for determination of baricitinib in plasma, and Its application in a pharmacokinetic study in rats," Molecules [Basel, Switzerland], vol. 25, issue 7, p. 1600, April, 2020.

[34] S. Gandhi, B. Kapoorm, " Development and validation of UV spectroscopic method for estimation of baricitinib," Journal of Drug Delivery and Therapeutics, vol. 9, issue 4-s, pp. 488-491, August, 2019.

[35] S.M ohan, N. Srinivasarao, K. Lakshmi, "Development and validation of a stability indicating related substances of baricitinib by RP-HPLC and its degradation," Int. J. Manag. Hum, vol. 4, issue 2, pp. 4-9, October, 2019.

[36] F. Breedveld, "Therapeutic monoclonal antibodies," Lancet, vol. 355, issue 9205, pp. 735-740, February, 2000.

[37] P. Taylor, A. Adams, M. Hufford, et al., "Neutralizing monoclonal antibodies for treatment of COVID-19," Nature Reviews Immunology, vol. 21, issue 6, pp. 382-393, June, 2021.

[38] R. Gottlieb, A. Nirula, P. Chen, et al., "Effect of bamlanivimab as monotherapy or in combination With etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial," JAMA, vol. 325, issue 7, pp. 632-644, February, 2021.

[39] B. Webb, W. Buckel, T. Vento, et al., "Real-world effectiveness and tolerability of monoclonal antibodies for ambulatory patients with early COVID-19," medRxiv, vol. 8, issue 7, pp. ofab331, March, 2021.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.005

June 2022
Volume 2
Issue 1

Polyetheretherketone [Peek]: A Contemporary Modality In Cranio Maxillofacial Reconstruction

Nada M. Fahmy [1]

[1]Assistant Lecturer of Oral and Maxillofacial Surgery, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Arab Academy for Science Technology & Maritime Transport [AASTMT], Egypt.

Email: nada.m.fahmy@gmail.com

Received on, 17 January 2022 - Accepted on, 01 June 2022 - Published on, 16 June 2022

Abstract:

This descriptive review focuses on the evolution of polyetheretherketone [PEEK] for the reconstruction of cranio-maxillofacial defects. This treatment modality is now trending and growing throughout the different aspects of the oral and maxillofacial specialty to include customized patient specific implants for reconstructive surgeries, and a material that is used in dental implants. The PEEK implants are created using computer tomography [CT]to reconstruct the defect either in the midface or cranial defects and match with the opposite side, all implants were secured using screws. Cases were followed up for 12 months, and there were no postoperative problems. This came to an end that PEEK is considered as a safe and good implanted bone substitute for the fixation of complex defects of the cranio-maxillofacial.

Key words: *cranio-maxillofacial reconstruction, polyetheretherketone [PEEK], facial deformities, patient specific implant [PSI]*

Introduction :

Overcoming problems of facial asymmetry of patients suffering from facial deformities resultant of trauma or tumor ablation is essential to achieve optimum results and patient satisfactions.[1] The desire for defect reconstruction in the best manner is challenging but possible while still saving the time needed in surgical intervention and is of a paramount importance to surgeons for enhancing patients end-results and overall health.[2] Several autografts and alloplastic materials have been used in cranio-maxillofacial [CMF] reconstruction.[3]

Treatment modalities of cranio-maxillofacial defects:

Autogenous bone grafts such as; calvarial bone, Rib bone grafts, iliac bone grafts, fibula bone grafts, embrace many advantages resembling resistance to infections, radio-transparency, growth potential with no additional financial burden on the patient and have been used all the time in reconstructive techniques of traumatic and congenital deformities in the maxillofacial and craniofacial region. [4,5,6]

Autogenous bone grafts are ideal for small, simple, and easily contoured defects. [7] However, they show important downsides such as donor site morbidity, time consuming harvests, and increased operative time. [7] As the defects become larger and more complex, the search for a more suitable non-toxic, biocompatible, and biologically inert material that would mimic the nature of bone tissue was mandatory. [7]

A significant advantage of alloplastic grafts is the lack of donor site morbidity as seen with autogenous grafts. Alloplastic grafts have also become easily and readily available for use. [8] Metals, ceramics, polymers, composites and numerous alloplastic materials are constructed using Additive Manufacturing [AM] techniques and are used extensively in orthopedic and reconstructive surgeries. [2]

The use of metallic implants [such as gold, tantalum, titanium alloys, stainless steel, and cobalt chromium] have been commonly seen all over medical institutes as permanent prosthesis for knee and hip replacements, cranio-maxillofacial prosthesis and dental implants. With the evolution of 3D printing technology, the custom-made titanium implants directly printed and applied have been reported to better accommodate challenging CMF surgical defects and to restrict the utilization of the traditional hand-shaped titanium mesh. [3,9]

Titanium is considered most compatible material and still a widely used, successful standard modality to repair bone fracture sites in the cranio-maxillofacial regions, as its osteo-inductive privilege to beneficially promote bone formation due to its titanium oxide layer. [9] However some adverse effects has been published such as[9,10]; difficulty of removal due to fibrous tissue encapsulation, their strength and elastic modulus surpasses that of normal human bone tissues and could result in a stress shielding counter effect leading to prosthetic loosening.[8,9] Other hazards have been encountered during the use of titanium meshes and metallic prostheses, which include hypersensitivity to titanium, the difficulty of design in complex cases, and injury resulting from its sharp edges.[9,10]

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.006

Metallic hardware's drawbacks have led to the rise of ceramics as an alternative reconstructive material. Calcium phosphates and glass ceramics are the most used. They are beneficial in their ability to form an appetite layer on its surface when exposed to physiological fluids in vivo or stimulated body fluids, [11] biocompatible and therefore possess a low toxicity profile. [12]

Due to the constraints witnessed when handling metallic and ceramic biomaterials, the use of polymers as a viable alternative is on the rise as of recently. A large number of polymers, such as ultrahigh molecular weight polyethylene [UHMWPE], polymethyl methacrylate [PMMA], polylactide [PLA], polyglycolide [PGA], and hydroxyapatite [13] are example of some of the most commonly used in various biomedical applications. However, only a limited number of polymers have been used for bone replacement purposes as they tend to be too flexible and too weak for load-bearing implants orthopedic applications. [13]

Methyl Methacrylate [MM] is the most extensively used alloplastic material for minor defects due to its strong solid and inexpensive nature. [14] The material is affordable and easy to use; however, it is alarming since it shows some exothermic reactions high risk of infection. [14]

Calcium phosphate ceramics [e.g., hydroxyapatite] are often used as bone void filler in oral surgery. Its granules or putty pastes used in dental application as they are biocompatible and osteoconductive, and can be placed manually to fill bone defects. [11] Nevertheless, their mechanical brittleness and the impossibility for direct implant fabrication limit their use. [11] Overcoming this problem, the introduction of HA inside biodegradable polymeric matrices improves the bioactivity of the implants and could even endow the composite biomaterials with osteo-inductivity. [12]

The ideal material has not been discovered yet, but among the various alloplastic materials, polyetheretherketone [PEEK] has been a popular choice for the Patient Specific Implant [PSI].[15,2,3] The most universally used PEEK coating, bioactive material, is Hydroxyapatite [HA].[15] HA [chemical formula Ca10[PO4]6[OH]2] is the most broadly used calcium phosphate-based bioceramic, which significantly resembles human mineral bone and has a high mean bone-implant contact contributes to osseointegration.[16]

Customized Patient Specific Implant

Over the past years, the rapid growth of 3D modelling and printing technologies are revolutionizing numerous surgical fields.[2] The cranio-maxillofacial surgeons have been one of the most important beneficiaries as facial computerized tomography [CT] scans are conducted to evaluate the degree of tissue damage and to perform virtual pre-operative surgical planning to design and print plastic anatomical models employed to manually adapt a standard implant to anatomically reconstruct the patients' fractured bones. Patient Specific Implant [PSI] can be an efficient treatment option that fits accurately within the anatomy of the defect. [17] The rise of Patient Specific Implant led to many developments in the medical industry. [17] It shows many advantages like less operation time and the ability to incorporate dental implants and direct rehabilitation. However, extra coast as well as extra processing time are required. [2,17]

The use of Virtual Surgical Planning [VSP] and navigation in fabrication of Customized Patient Specific Implant [PSI] [2]

Multi-planar computer tomography [CT] scans associated with virtual surgical planning [VSP] computer- aided design [CAD] / computer-aided modeling [CAM] help the operator to remodel the approach and execution of complex head and neck resections and reconstructions. [3] It offers several advantages including increased accuracy of reconstruction, reduced surgery and graft ischemia time, improved patient satisfaction and ease of use. [2]

The use of computer technology in the pre-surgical planning phase includes the transfer of CT scan data in digital information and communications in medicine [DICOM] format through the CAD/CAM software, where the data can be assessed and handled virtually in all three dimensions. A simulated surgical plan can then be formulated using several methods, including segmentation of the affected areas; mirror imaging the opposite normal side; reduction of the affected bone in 3D space; virtual osteotomies; or insertion of anatomic structures as required. Moreover, fabrication of stereolithographic models from information of the virtual reconstructions permits preoperative planning of osteotomies, plate contouring, and eases the intraoperative contouring of bone grafts. Additionally, additive manufacturing [AM] for the printing process, 3D printer scan reads and analyzes CT scan data and creates customized surgical models from the information, if necessary. Both VSP and 3D models are used to precisely place the ideal amount, shape, and dimensions of autologous tissue or bio-prosthetic material needed for reconstruction. [2]

Finally, the CAD/CAM software permits the conversion of the virtual reconstruction information back into DICOM format in order to transfer data to a surgical navigation system to be used intraoperatively that could reduce the incidence of postsurgical complications due to a wrong positioning or orientation of bone grafts, plates, or fixation screws. [2]

Polyetheretherketone [PEEK]

Polyetheretherketone has been introduced as an implant material in several medical applications since the 1990s owing to its close-to-bone elasticity, high stability, low density [1.32 g/cm3] and insolubility. [18,19] Its use and popularity have also taken over the dental field. [19,20] Polyetheretherketone has been used in aircrafts, automotive and electrical industries over the past 20 years [20,21] PEEK is simply a semicrystalline polyaromatic thermoplastic linear polymer in ether and ketone linkages that presents an exceptional combination of biocompatibility, [22] stiffness, durability and natural

resistance along with resistance to high temperatures and radiation. [14,22]

It has been stated by manufacturing companies that PEEK possesses bone-like thermal conductivity of 0.4W/Km.[23] Consequently, because it resembles cortical bone it has become safe, predictable and stable option. [24,25]

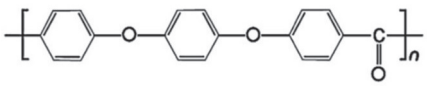
The use of PEEK in implants has been available since 1998. Initially it was used for spinal surgery and hip replacements until it became more and more employed in CMF surgery. PEEK has shown massive success in the treatment of cervical disk problem. [25-27] Explicitly, in anterocervical fusion, PEEK has been alternatively used to autogenic bone grafts and titanium cages.[27,28] The use of PEEK as plates and screws for fracture fixation has increased due to its biocompatibility.[29,30] It has also been utilized in the form of PSI for the reconstruction of cranio-maxillofacial bone defects.[30]

Physical and biological properties of unfilled PEEK biomaterial and PEEK composite

Polyetheretherketone is a polyaromatic semicrystalline thermoplastic material, with typically 30-35% crystallinity. The material bosses a melting temperature in the vicinity of 343°C, a crystallization peak of ~160°C and a glass transition temperature of ~145°C. These melt temperatures allow PEEK material to be formed by either injection molding or extrusion using conventional methods. [30,31] Its thermal properties make it durable in human body. [31,32]

According to their melt flow index [MFi] and molecular weight [Mn], PEEK- materials are divided in three material grades. [32] All follow the same standard formula [-C6H4-O-C6H4-O-C6H4-CO-] n:[18,32,33] [Fig. 1]

- LT1-standard grade [MFi-3.4; Mn = 115.000].
- LT2-optimized grade for melt strength and medium melt viscosity [MFi-4.5; Mn = 108.000].
- LT3- high-flow grade for injection molding thin-walled parts.



[Courtesy to Bathala L et al.]

Fig. 1. chemical structure of PEEK

One of the most valuable advantages of the PEEK polymer is its compounding ability either to increase its innate strength or to improve its biocompatibility. This advantage is better performed in the biomedical fields with the utilization of the standard grade PEEK LT1 materials. [34,35] Amongst the first PEEK composites seen in biomedical applications was the carbon reinforced PEEK composite [CFR-PEEK].[35] Adding filler materials by compounding, in the form of short carbon or glass fibers, improves the strength of the natural unfilled polymer. Making it more powerful in withstanding greater stress demanding applications for bone replacement. [35,36]

PEEK composite devices were first applied for fracture fixation, using carbon reinforcement in a PEEK matrix. [34,35]

Carbon reinforced PEEK composites are characterized by stiffness and high strength due to the presence of fibers. [37] Carlile et al. [1989] examined the effect of temperature on strength for fiber and matrix lay-ups. [38] They found that most of its characteristic properties were retained at varying temperatures up to 141 °C [the glass transition temperature]. On the other hand, as the crystalline melting transition temperature is reached at around 343 °C, CFR PEEK demonstrates high levels of toughness across different testing techniques such as fracture resistance, weight impact and post-impact compression. [34-36] CFR-PEEK showed to be chemically inert, nontoxic and insoluble in all conventional solvents at room temperature, except in 98% sulfuric acid. [37,38]

Glass-fiber reinforced PEEK composites [GFR-PEEKs] is another variation of PEEK composites. [39] Chopped E-glass fibers with an elastic modulus comparable to that of cortical bone are dispersed randomly within the PEEK matrix. [40] Panayotov et al. demonstrated a significant increase in elastic modulus of the bioactive PEEK composites in contrast with carbon fiber and glass fiber additives. Moreover, soaking PEEK/carbon fiber composites in physiological Saline up to 5000hrs duration followed by compression tests confirm its stability. [40]

Polyetheretherketone and its composites can undergo steam sterilization repeatedly without losing their mechanical characteristics. [2,30-32] One of the methods of sterilizing medical devices is through gumma radiation. [31] As for polymeric materials, they often become weakened and embrittled when exposed to radiation as a result of induced cross-linking and/or chain scission. PEEKs resilient chemical structure makes it well tolerated to gumma radiation. [31]

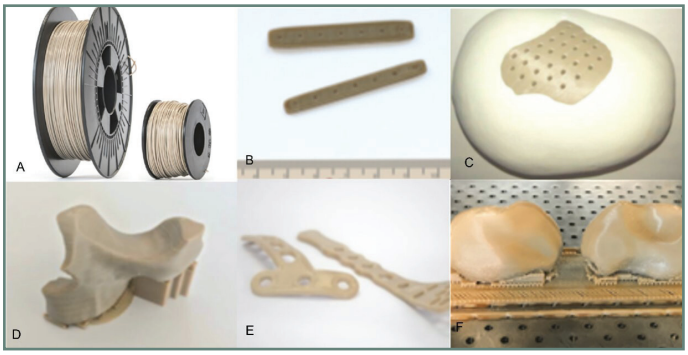
Polyetheretherketone Implants in Cranio-Maxillofacial Reconstruction:

Honigmann et al. [2018] [2] represented the PEEK filament used in the printing process as a semicrystalline polymer having a density of 1.30 g/cm3 and tensile strength of 97MPa [Fig. 2a]. This filament combines the perfect amount of strength, toughness, and stiffness with great chemical resistance. Moreover, it is highly stable against hydrolysis, and is sterilizable. [2] The results revealed that the 3D printed PEEK PSI were even smooth devoid of irregularities. [2] No discoloration [improper crystallization] or black specks formation were noticed. All the 3D printed parts were assessed for certified sterilization test and passed without any deformation. [2] Five different PEEK structures were fabricated for the cranio-maxillofacial reconstruction:[2]

1. Osteosynthesis plate. [Fig. 2b]
2. Cranioplasty PSI for repair of defects in the cranial vault. [Fig. 2c]
3. Lightweight midface-zygomatic bone PSI with support structures for immediate replacement. [Fig. 2d]

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.006

4. Small fragment PSI osteosynthesis plates. [Fig. 2e]
5. Prosthetic implant for scaphoid bone replacement. [Fig. 2f]



[Courtesy to Honigmann et al.]

Fig. 2. A] Medical grade PEEK filament-3Dprinting. B] Osteosynthesis plate. C] Cranioplasty PSI for repair of defects in the cranial vault. D] Lightweight midface-zygomatic bone PSI with support structures for immediate replacement] E] Small fragment PSI osteosynthesis plates F] Prosthetic implant for scaphoid bone replacement.

[a] Polyetheretherketone in Cranial Bone Reconstruction

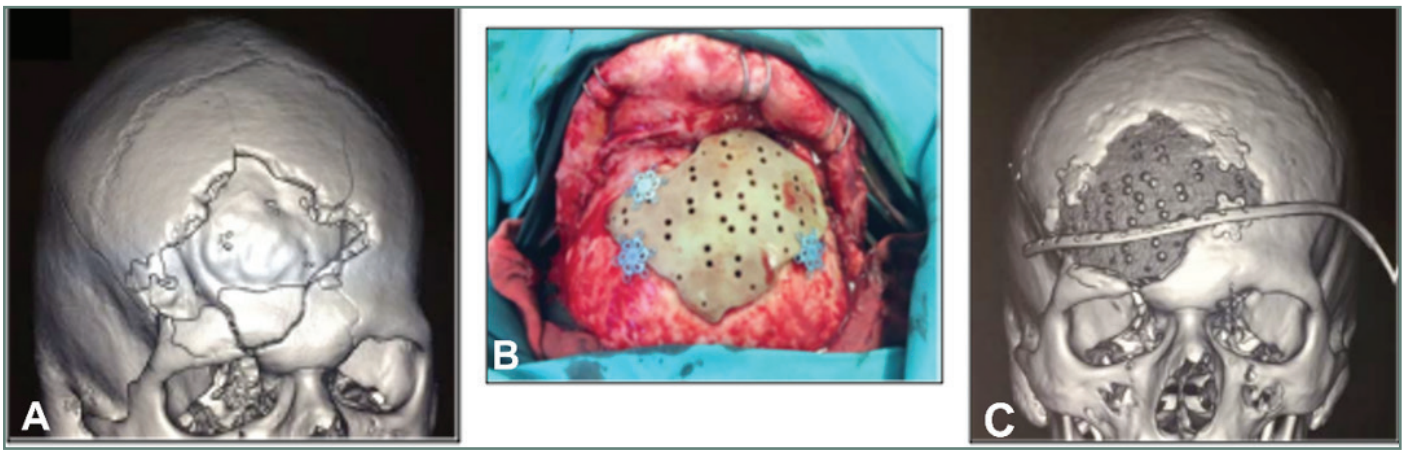
During decompressive craniectomy, cranial defects usually arise and a segment of the cranial vault is excised for surgical access to decrease the intracranial pressure that can be caused by surgical intervention secondary to chronic infection or uncontrolled osteoradionecrosis, several types of traumas, tumors, infections and congenital cranial anomalies causes. [41,42] The frontal bone is so strong and it requires high velocity to fracture from 800 to 2,200lb. [41,42]

Cranio-plastic techniques have been reported previously in prehistoric times and many materials were available at that time, some of which are still being used to date. [104] The "gold standard" for cranial vault reconstruction has always been Autogenous bone grafts of calvaria, rib grafts, or iliac source or tissue free grafts, but the major problem was always local resorption[43] inability to be used with complicated multi-fragmented fractures, ex. gun shots injury, poor bone quality after chemotherapy and radiotherapy [44,45], limited bone availability and shaping in addition to donor site morbidity.[43]

There is no such thing as a perfect ideal material, but PEEK patient specific implants have been highly appraised in the reconstruction following craniofacial tumors resection or traumatic brain injuries [18,45,46] and it is supplied as single or multiple pieces and conventional fixation. It showed massive success because of its structural durability at high temperatures and radiation maintained by the polymer. [21,22,23] It is sterilizable in moist or dry heat without dimensional changes. [35]

In 2015, O'Reilly et al. [47] made a 6-year retrospective review of cranioplasty procedures in nineteen patients receiving 22 CT-based PEEK cranioplasty. Three patients had re-operation following PEEK plate reconstruction. The authors concluded that use of CAD/CAM PEEK plate for cranial reconstruction has several benefits: ease of insertion with excellent anatomical precision and aesthetic results; potential intra-operative time saving; and the plate is also easily modified in the operating room. [47]

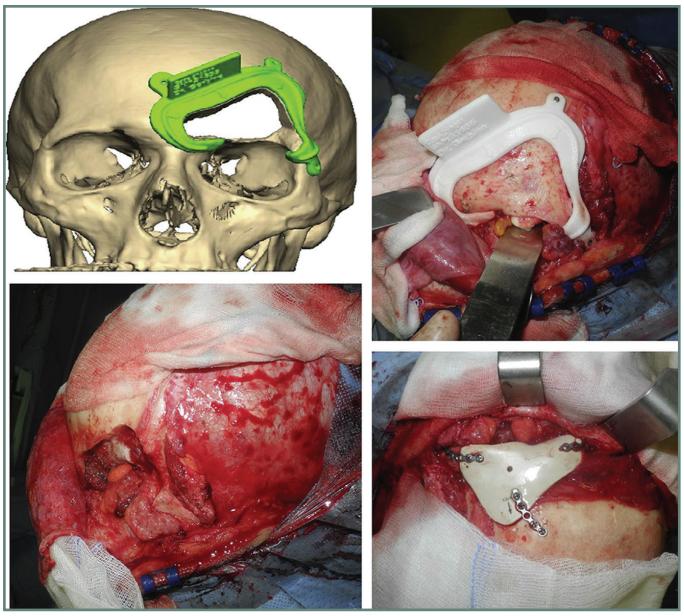
Malivuković et al., described a case [48] of a 21-year-old male patient victim of a gunshot injury to the frontal region, [48] 6 months after the primary surgical debridement, removal of bone fragments and absence of signs of infection. The patient presented with an intricate defect of the skull involving both frontal and sphenoidal bones. The decision was made to use 3D fabricated implant using a non-resorbable thermoplastic material PEEK- OPTIMA®. [48] [Fig. 3]



[Courtesy to Malivuković et al.]

Fig. 3. A] Preoperative computed tomography showing a complex defect of the skull B] cranioplasty was performed through a bi-coronal approach with the prefabricated 3D PEEK OPTIMA® implant and fixed after preparing the bone edges with titanium screws and stars C] Computed tomography [3D recon-striction] postoperatively showing the fixed PEEK OPTIMA® implant filled the bone deficiency.

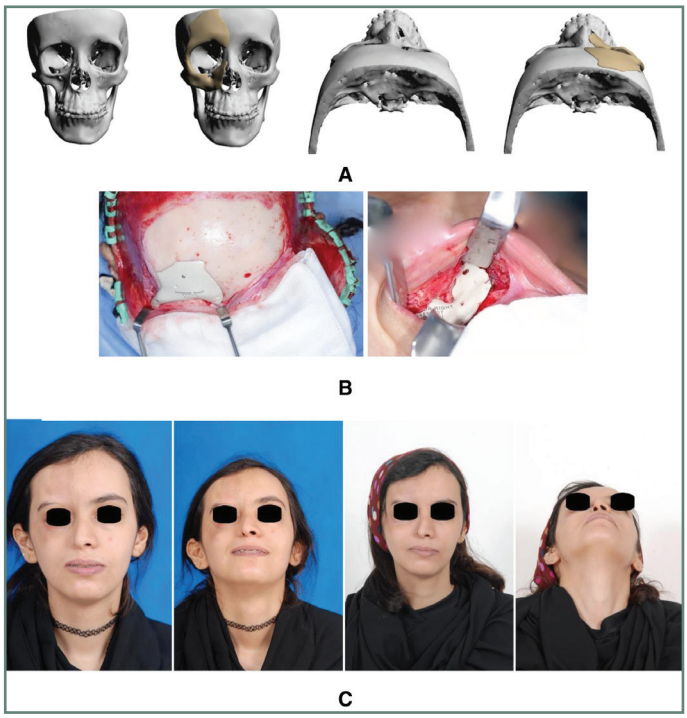
Gerbino et al. [49] described their experience with the PEEK PSIs on a group of patients that underwent cranio-orbital reconstruction as being cosmetic and with mechanically favorable outcomes. One of those patients was a 46-year-old man with fronto-ethmoidal sinusitis following fronto-orbital osteoma involving both anterior and posterior walls of the frontal sinus. The patient had gone through one-step resection and primary reconstruction with polyetheretherketone [PEEK] patient-specific implant [PSI]. [Fig.4]



[Courtesy to Gerbino et al.]
Fig. 4. A]
Virtual planning of the resection with computer-generated cutting guide. B] Intraoperative view of the cutting guide] C] Exclusion and obliteration of the naso-frontal recess and preparation of the pericranial flap] Intraoperative view of the implant fits into the defect, pericranial flap rotated under the implant.

The objective of surgical treatments of frontal bone fractures is to restore the front anatomic contour especially in severe defects involving the front orbital region, [41,47,48] besides preventing infection of intracranial components and frontal sinuses. [47,48]

In another case reported by Nasser Alasseri and Ahmed Alasra,[50] PEEK was used as a reconstructive method for craniosynostosis birth defects conditions. A 23-year-old female with a diagnosis of Parry-Romberg syndrome that lead to hypoplasia in the right side of her face. She had a history of fat grafting and fillers to cover the defect with unacceptable results. [50] The patient underwent PEEK PSI reconstruction for her frontal bone, zygoma, and maxilla on the right side of her face through bicoronal and vestibular approaches. Patient satisfaction has revealed excellent postoperative results. [50] [Fig. 5]



[Courtesy to Nasser Alasseri and Ahmed Alasra.]
Fig. 5. Parry-Romberg syndrome case. A]3D reconstruction of the CT showing the defects andthe planned implants. B] Intraoperative views of the implants. C]Pre- and postoperative photographs of the patient.

[b] PEEK in Midface Complex Reconstruction

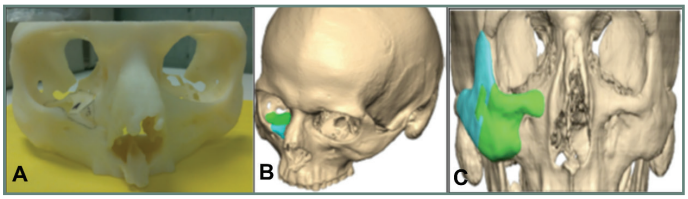
Amongst the first facial areas to reveal aging signs is the midface.[51] Midface is an area bounded by the canthal and oral commissure,[51] Deficiencies of the midface either secondary to tumor removal, traumatic injury, bony insufficiency from birth or skeletal resorption with aging that will exaggerate the seeming age of such areas,[51] as loss of volume occurs in the bony and soft tissue skeleton it produces a widespread orbital opening and less anterior projection, this minimizes the overall projection of the cheek and decreases bone support available for the overlying soft tissue structures.[51]

Orbito-zygomatic complex fractures are one of the most frequently seen injuries of the craniofacial skeleton [52] resulting from personal violence, road traffic accidents, falls and sport injuries. [49,52] Restricted eye movement, altered globe level, diplopia, visual impairment, circumorbital ecchymosis and altered sensation over the division of the infraorbital nerve are the main encountered problems in orbital floor fractures.

All these signs need immediate surgical intervention. [52] M.L. Goodson et al.[53] fabricated two-pieces PEEK implants; one zygomatic implant [as a two-piece jigsaw] was used in treating a patient with flattened cheeks after a fracture of the right zygomatic complex, and the other implant for a patient with a defect in the inferior orbital rim and hypoglobus after presentation of a fracture of the orbital floor and rim.[53] In both cases, the implants were designed on a stereolithographic model using CT.[53][Fig. 6] The two-piece design

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.006

allowing segments of the implant to be inserted through different paths. Both patients were followed up for 12 months, the implants were easily inserted with no need for adaptation and no signs of rejection were reported using the two-piece PEEK implants for orbito-zygomatic reconstruction. [53]

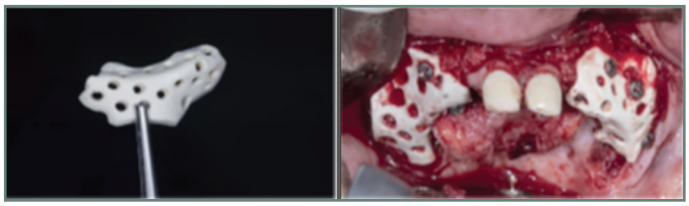


[Courtesy to M.L. Goodson et al.]

Fig. 6. A] Stereolithographic model for orbital rim and floor implant B] Two-piece orbital floor and rim implant] C] Zygomatic implant; [up to the zygomaticofrontal suture, infraorbital rim, zygomatic arch, and piriform rim]

Zain et al. [54] in their pilot study, fabricated PSI of PEEK while using it to contain the bone graft within and reconstructing the bony defect for future implant rehabilitation, the significant difference in bone density between immediate and 4 months postoperative C.T. is a sign of ongoing bone remodeling and calcification. [54] The technique was regarded as a promising solution to reconstruct the maxillary intrabony defects without dispersion of the graft into the sinus cavity. However, soft tissue dehiscence was evident, and infection occurred in some cases that should have been considered in the PSI design and material. [54]

Mounir et al. [55] conducted a randomized clinical trial, including two equal groups of patients who had a partial or completely edentulous maxillary alveolar ridge defect following teeth loss. Eight patients in each group who underwent 3D ridge augmentation using either a titanium mesh [control group] or a patient specific milled PEEK mesh [study group] utilizing a 50:50 mixture of autogenous bone harvested from the iliac crest of each individual patient and xenogeneic bone. [55] [Fig. 7] Collagen membrane was then applied on top of the meshes in both groups. They reported that titanium mesh exposure in one case of the control group at two weeks resulted, but this complication was not found in the PEEK group. [55] This exposure, however, did not result in a compromised regeneration and implants were successfully installed in the newly regenerated bone. [55]



[Courtesy to MOUNIR et al.]

Fig. 7. 3D PEEK mesh in place fixed with bi-cortical titanium screws.

[C] PEEK in Mandibular Reconstruction

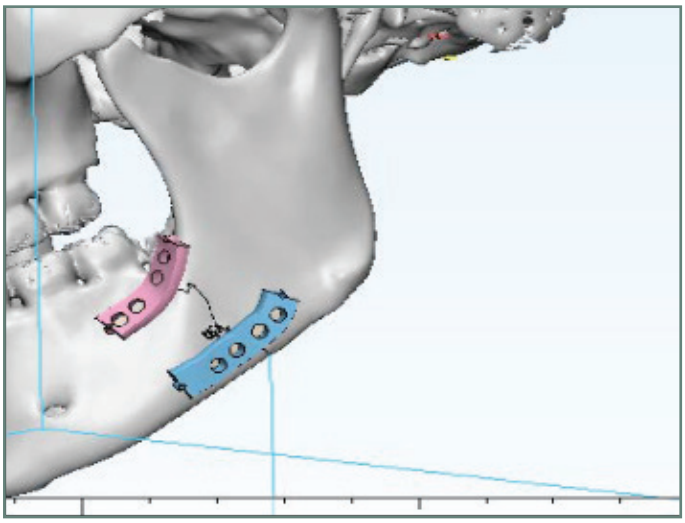
The mandible is only one of its kind bones having a complex role in esthetics of the face and functional occlusion. Because of the prominent position of the lower jaw, mandibular fractures are the most common fractures of the facial skeleton. It has been stated that fractures of the mandible account for 36% to 59% of all CMF fractures. [56]

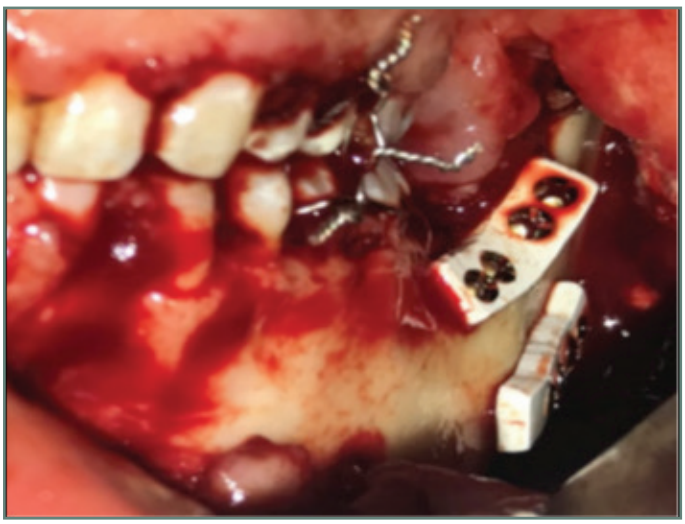
The fractured segments of the mandible are protected against micro motion under function leading to minimized inter-fragmentary strains.[56] Therefore, a mechanically stable fixation permits adequate bone repositioning and allows for functional healing.[56] The most accustomed mandibular reconstruction method, with a fibula free flap showed some limitations like second surgical harvested site, plate exposure, plate fracture, infections and vascular issues.[57]

With the introductory movement of computer-assisted mandibular reconstruction and the virtual planning to produce a PSI for bone replacement, three dimensional miniplates osteosynthesis and custom-made reconstruction of plates for fixation of reduced mandibular fractured segments,[57] leading to greater surgical precision, increasing the accuracy of pre-operative planning, reducing surgical time and better aesthetic result.[57] Owing to its bone-like elasticity [elastic modulus: three-four GPa], PEEK [polyetheretherketone] is considered a practical alternative material. Its use as an implant material has been successfully evident in several medical aspects since the 1990s [18,19] due to its superior stability, minimal density [1.32 g/cm3] and lack of solubility. [21,22]

Dessoky et al. [30] used in their study PEEK in mandibular fractures. They included patients suffering from recent, uninfected, non-comminuted mandibular body fracture, unfavorable fracture that demands open reduction and internal fixation. [30] Three-dimensional reconstruction of the segmented mandible along with dental hard tissue was created and virtual reduction of mandibular fracture was verified. [30] Inter maxillary fixation [IMF] was temporarily secured to offer proper occlusion that worked as a guide for fracture reduction. Placement of the custom-made PEEK plates in place and fixed by mini screws [Fig. 8]. They stated that the occlusion was productively achieved in all patients. After six months followed up postoperatively, they concluded that Fixation of mandibular fracture with custom made PEEK plate is anti-microbial and provides satisfying clinical and radiographically. [30]

El-Hawary et al. [57] reported a case of a 24-year-old male with mandibular 'follicular ameloblastoma' and parathesia. The authors followed a guided protocol; guided resection, guided alignment of the reconstruction plate secured to digitally mirror-imaged PEEK.[57] Their aim was to evaluate the efficiency of CAD/CAM to fabricate PEEK to duplicate both of the exact anatomic position and the configuration of the resected mandibular condyle, post segmental tumor resection. [57] However, they stated that the degree of accuracy between the virtual planned condylar location and that surgically executed was judged as good to excellent in all operated cases.[57] They considered the custom designed PEEK unit simply and efficiently reformed the deficient condyle position and configuration. Yet, the success of preoperative virtual planning and surgical execution is mainly dependent upon the resected proximal mandibular segment anteriorly. [57]

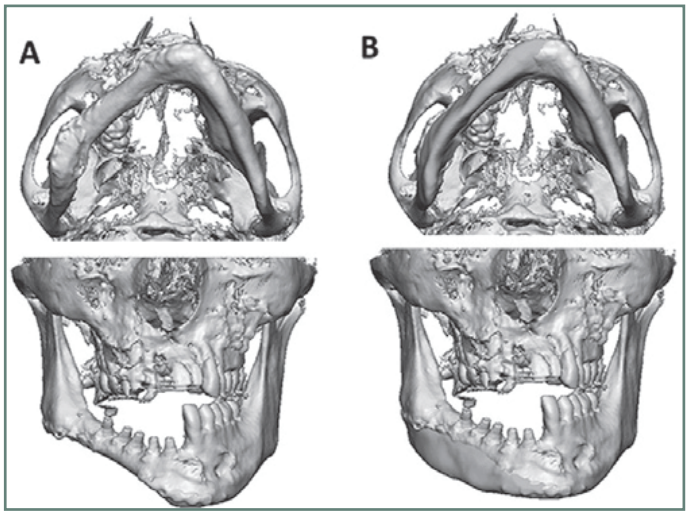




[Courtesy to Dessoky et al and M. Berrone et al.]

Fig.8. A] PEEK custom plates after being planned on the virtually reduced mandible and fixation of PEEK plates intraoperatively.

M. Berrone et al.[58] in their report cases included a 27-year-old man referred for correction of facial asymmetry as a result of major trauma with loss of hemi mandible which has been reconstructed primarily with a fibula free flap.[58] Using the 3D virtual model of the mandible and the mirroring technique, a PEEK PSI [Fig. 9] was fabricated to restore the symmetry of the mandible.[58] After eight months of follow-up of the implant positioning in the fibula and provisional dental restoration to stabilize the maxillo-mandibular relationship, there were no clinical or radiological complications.[58]



[Courtesy to M. Berrone et al.]

Fig. 9. [A] 3D reconstruction of the craniofacial skeleton: virtual inferior view and frontal view. [B] Virtual inferior view and frontal view after positioning of the custom-made prosthesis.

Conclusions:

In the scope of this review, it can be concluded that:

1. 1. PEEK is biocompatible, adapts anatomically, remains still stiff and stable and is nonmagnetic.
2. 2.PEEK is regarded as a safe and good implanted bone substitute for the treatment of complex defects of the cranio-maxillofacial in comparison to alternative alloplastic materials.

Conflict Of Intrest:

The authors acknowledged that they do not have any conflict of interest.

References:

[1] G. Saponaro, P. Doneddu, G. Gasparini, et al., "Custom made onlay implants in peek in maxillofacial surgery: a volumetric study," Childs Nerv Syst, vol. 36, issue2, pp. 385-391, February, 2020.

[2] P. Honigmann, N. Sharma, B. Okolo, U. Popp, "Patient-Specific Surgical Implants Made of 3D Printed PEEK: Material, Technology, and Scope of Surgical Application," Biomed Res Int. vol.2018, pp. 1-8, March, 2018.

[3] C. Maas, G. Merwin, J. Wilson, M. Frey, M. Maves, "Comparison of biomaterials for facial bone augmentation," Arch Otolaryngol Head Neck Surg, vol 116, issue 5, pp. 551-556,

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.006

May, 1990.

[4] I. Jackson, G. Helden, R. Marx, "Skull bone grafts in maxillofacial and craniofacial surgery," J Oral MaxillofacSurg, vol 116, issue5, pp.949-955, May, 1986.

[5] M. Berrone, C. Aldiano, M. Pentenero, S. Berrone, "Correction of a mandibular asymmetry after fibula reconstruction using a custom-made polyetheretherketone [PEEK] onlay after implant supported occlusal rehabilitation," Acta Otorhinolaryngoltal,vol.35,issue4,pp.285-288,October,2015.

[6] Y. Tie, D. Wang, T. Ji, C. Wang, C. Zhang, "Three-dimensional finite-element analysis investigating the biomechanical effects of human mandibular reconstruction with autogenous bone grafts," J Craniomaxillofac Surg, vol. 34, issue 5, pp. 290-298, July, 2006.

[7] J. Park, K. Lee, J. Shim, S. Yoon, W. Choi, J. Doh, "Large defect may cause infectious complications in cranioplasty," J Korean Neurosurg Soc, vol. 42, issue 2, pp. 89-91, August, 2007.

[8] A. Jardini, M. Larosa, R. MacielFilho, C. Zavaglia, L. Bernardes, C. Lambert, et al., "Cranial reconstruction: 3D biomodel and custom-built implant created using additive manufacturing," J Craniomaxillofac Surg, vol. 42, issue 8, pp.1877-18, December, 2014.

[9] H. Egusa, N. Ko, T. Shimazu, H. Yatani, "Suspected association of an allergic reaction with titanium dental implants: a clinical report," J Prosthet Dent, vol. 100, issue 5, pp.344-347, November, 2008.

[10] J. Kuttenberger, N. Hardt, "Long-term results following reconstruction of craniofacial defects with titanium micro-mesh systems," J Craniomaxillofac Surg, vol. 29, issue 2, pp.75-81, April, 2001.

[11] L. Zhang, G. Yang, B. Johnson, X. Jia, "Three-dimensional [3D] printed scaffold and material selection for bone repai," Acta Biomater, vol. 84, issue 1, pp.16-33, January, 2019.

[12] R. Ma, T. Tan, "Current strategies to improve the bioactivity of PEEK," Int J Mol Sci, vol.15, issue 4, pp. 5426-5445, April, 2014.

[13] P. Frassanito, L. Massimi, G. Tamburrini, F. Bianchi, A. Nataloni, V. Canella, et al., "Custom-made hydroxyapatite for cranial repair in a specific pediatric age group [7-13 years old]: a multicenter post-marketing surveillance study," Childs Nerv Syst, vol. 34, issue 11, pp.2283-2289, November, 2018.

[14] A. Ridwan-Pramana, S. Idema, S. TeSlaa, F. Verver, J. Wolff, T. Forouzanfar, et al., "Polymethyl Methacrylate in Patient-Specific Implants: Description of a New Three-Dimension Technique," J Craniofac Surg, vol. 30, issue 2, pp.408-411, March, 2019.

[15] A. Pinheiro, F. Junior, M. Gerbi, L. Ramalho, C. Marzola, E. Ponzi, "Effect of Low-Level Laser Therapy on the Repair of Bone Defects Grafted with Inorganic Bovine Bone," Braz Dent J," vol. 14, issue 3, pp.177–218, March, 2003.

[16] S. Järvinen, J. Suojanen, E. Kormi, T. Wilkman, A. Kiukkonen, J. Leikola, et al., "The use of patient specific polyetheretherketone implants for reconstruction of maxillofacial deformities," J Craniomaxillofac Surg, vol. 47, issue 7, pp.1072-1076, July, 2019.

[17] S. Barkarmo, A. Wennerberg, M. Hoffman, P. Kjellin, K. Breding, P. Handa, et al., "Nano-hydroxyapatite-coated PEEK implants: a pilot study in rabbit bone," J Biomed Mater Res, vol. 101, issue 2, pp. 465-471, February, 2013.

[18] M. Chae, W. Rozen, P. McMenamin, M. Findlay, R. Spychal, D. Hunter-Smith, "Emerging Applications of Bedside 3D Printing in Plastic Surgery," Front Surg, vol 16, issue 2, p.25, June, 2015.

[19] S. Kurtz, J. Devine, "PEEK biomaterials in trauma, orthopedic, and spinal implants," Biomaterials, vol. 28, issue 32, pp. 4845-4869, November, 2007.

[20] A. Schwitalla, W. Muller, "PEEK dental implants: a review of the literature," J Oral Implantol, vol. 39, issue 6, pp.743-749, December, 2013.

[21] M. Andreiotelli, H. Wenz, R. Kohal, "Are ceramic implants a viable alternative to titanium implants? A systematic literature reviews," Clin Oral Implants Res vol. 20, issue s4, pp. 32-47, September, 2009.

[22] A. Schwitalla, T. Zimmermann, T. Spintig, I. Kallage, W. Müller, "Fatigue limits of different PEEK materials for dental implants," J Mech Behav Biomed Mater vol. 69 , pp.163-168, May, 2017.

[23] K. Jockisch, S. Brown, T. Bauer, K. Merritt, "Biological response to chopped-carbon-fiber-reinforced peek," J Biomed Mater Res vol. 26, issue 2, pp.133-146, February, 1992.

[24] B. Lethaus, Y. Safi, M. terLaak-Poort, A. Kloss-Brandstätter, F. Banki, C. Robbenmenke, et al., "Cranioplasty with customized titanium and PEEK implants in a mechanical stress model," J Neurotrauma vol. 29, issue 6, pp. 1077-1083, April, 2012.

[25] N. Patel, B. Kim, W. Zaid, "Use of virtual surgical planning for simultaneous maxillofacial osteotomies and custom polyetheretherketone implant in secondary orbito-frontal reconstruction: Importance of restoring orbital volume," J Craniofac Surg vol. 28, issue 2, pp. 387-390, March, 2017.

[26] S. Ersanli, C. Karabuda, F. Beck, B. Leblebicioglu, "Resonance frequency analysis of one-stage dental implant stability during the osseointegration period," J Periodontol, vol. 76, issue 7, pp.1066–1071, July, 2005

[27] M. Kim, K. Boahene, P. Byrne, "Use of customized polyetheretherketone [PEEK] implants in the reconstruction of complex maxillofacial," Arch Facial Plast Surg, vol. 11, issue 1, pp. 11-53, January, 2009.

[28] A. Telfeian, K. Moldovan, E. Shaaya, S. Syed, A. Oyelese, J. Fridley, et al., "Awake, Endoscopic Revision Surgery for Lumbar Pseudarthrosis After Transforaminal Lumbar Interbody Fusion: Technical Notes," World Neurosurg, vol. 136, pp. 117-121, April, 2020.

[29] C. Morrison, R. Macnair, C. MacDonald, A. Wykman, I. Goldie, M. Grant, "In vitro biocompatibility testing of polymers

for orthopaedic implants using cultured fibroblasts and osteoblasts," Biomaterials, vol. 16, issue 13, pp. 987-992, September, 1995.

[30] A. Padolino, G. Porcellini, B. Guollo, E. Fabbri, et al., "Comparison of CFR-PEEK and conventional titanium locking plates for proximal humeral fractures: a retrospective controlled study of patient outcomes," Musculoskelet Surg, vol. 102, issue 1, pp. 49-56, October, 2018.

[31] N. Dessoky, A. El-Mahallawy, M. Fahmy, M. Khalil, "Use of custom-made peek plates for treatment of mandibular fracture," Alexandria Dent J, vol. 45, issue 2, pp. 125-128, April, 2020.

[32] G. Skariah, G. Zachariah, "Polyetheretherketone: A Crystalline Non-Metallic Plate: Past, Present and Future-A Review," J Adv Med Dent Scie Res, vol. 7, issue 7, pp. 31-35, July, 2019.

[33] L. Bathala, V. Majeti, N. Rachuri, N. Singh, S. Gedela, "The Role of Polyether Ether Ketone [Peek] in Dentistry - A Review," J Med Life, vol. 12, issue 1, pp. 5-9, January, 2019.

[34] J. Fan, C. Tsui, C. Tang, C. Chow, "Influence of interphaselayer on the overall elasto-plastic behaviors of HA/PEEK biocomposite," Biomaterials vol. 25, issue 23, pp. 5363-5373, October, 2004.

[35] S. Ferguson, J. Visser, A. Polikeit, "The long-term mechanical integrity of non-reinforced PEEK-OPTIMA polymer for demanding spinal applications: experimental and finite-elementanalysis," Eur Spine J, vol. 15, issue 2, pp. 149-156, February, 2006.

[36] JSH. Bradley, GW. Hastings, C. Johnson-Nurse, "Carbon fibrereinforced epoxy as a high strength, low modulus material for internal fixation plates," Biomaterials vol. 1, issue 1, pp. 38-40, January, 1980.

[37] RK. Ponnappan, H. Serhan, B. Zarda, R. Patel, T. Albert, AR. Vaccaro, "Biomechanical evaluation, and comparison of polyetheretherketone rod system to traditional titanium rod fixation," Spine J, vol. 9, issue 3, pp. 263-267, March, 2009.

[38] EL. Steinberg, E. Rath, A. Shlaifer, O. Chechik, E. Maman, M. Salai, "Carbon fiber reinforced PEEK Optima—A composite material biomechanical properties and wear/debris characteristics of CF-PEEK composites for orthopedic trauma implant," J Mech Behav Biomed Mater, vol. 17, issue 1, pp. 221-228, January, 2013.

[39] DR. Carlile, DC. Leach, R. Moore, N. Zahlan, "Mechanical properties of the carbon fiber/PEEK composite APC-2/AS-4 for structural application. In: Newaz GM [ed]. Advances in Thermoplastic Matrix Composite Materials," Philadelphia: American Society for Testing and Materials, pp. 199-222, 1989.

[40] SW. Ha, M. Kirch, F. Birchler, KL. Eckert, J. Mayer, E. Wintermantel, et al., "Surface activation of polyetheretherketone [PEEK] and formation of calcium phosphate coatings by precipitation," J Mater Sci Mater Med, vol. 8, issue 11, pp. 683-690, November, 1997.

[41] MS. Abu Bakar, P. Cheang, KA. Khor, "Mechanical properties of injection molded hydroxyapatite–polyetheretherketonebiocomposite," Compos Sci Technol, vol. 8, issue 11, pp. 421-425, November, 2003.

[42] R. Schreurs, L. Dubois, AG. Becking, AG. Becking, L. Dubois, et al., "The use of cranial resection templates with 3D virtual planning and PEEK patient-specific implants: A 3-year follow-up," J Craniomaxillofac Surg, vol. 47, issue 4, pp. 542-547, April, 2019.

[43] ET. Camarini, JK. Tomeh, RR. Dias, "Reconstruction of Frontal Bone Using Specific Implant Polyether-Ether-Ketone," J Craniofac Surg, vol. 22, issue 6, pp. 2205-2207, November, 2011.

[44] PV. Giannoudis, H. Dinopoulos, E. Tsiridi, "Bone substitutes: an update," Injury, vol. 36, issue 3, pp. 20-27, November, 2005.

[45] IT. Jackson, C. Pellett, JM. Smith, "The skull as a bone graft donor site," Ann Plast Surg, vol. 11, issue 6, pp. 527-532, November, 1983.

[46] M. Punchak, LK. Chung, C. Lagman, TT. Bui, J. Lazareff, K. Rezzadeh, et al., "Outcomes following polyetheretherketone [PEEK] cranioplasty: Systematic review and meta-analysis," J Clin Neurosci, vol. 41, pp. 30-35, July, 2017.

[47] F. Jalbert, S. Boetto, F. Nadon, F. Lauwers, E. Schmidt, R. Lopez, "One-step primary reconstruction for complex craniofacial resection with PEEK custom-made implants," J Craniomaxillofac Surg, vol. 41, pp. 141-148, July, 2014.

[48] EB. O'Reilly, S. Barnett, C. Madden, B. Welch, B. Mickey, S. Rozen, "Computed tomography modeled polyether ether ketone [PEEK] implants in revision cranioplast," J Plast Reconstr Aesthet Surg, vol. 68, issue 3, pp. 329-338, March, 2015.

[49] A. Malivuković, N. Novaković, M. Lepić, L. Minić, N. Stepić, B. Đorđević, et al., "Cranial reconstruction with prefabricated 3D implant after a gunshot injury: A case report," Vojnosanit Pregl, vol. 73, issue 8, pp. 783-787, August, 2016.

[50] G. Gerbino, E. Zavattero, F. Zenga, FA. Bianchi, P. Garzino-Demo, S. Berrone, "Primary and secondary reconstruction of complex craniofacial defects using polyetheretherketone custom-made implant," J Craniomaxillofac Surg, vol. 43, issue 8, pp. 1356-1363, October, 2015.

[51] N. Alasseri, A. Alasraj, "Patient-specific implants for maxillofacial defects: challenges and solution," Maxillofac Plast Reconstr Surg, vol. 42, issue 1, pp. 1-8, December, 2020.

[52] WJ. Binder, B. Azizzadeh, "Malar and submalar augmentation," Facial Plast Surg Clin North Am, vol. 16, issue 1, pp. 11-32, February, 2008.

[53] G. Gerbino, FA. Bianchi, E. Zavattero, F. Tartara, D. Garbossa, A. Ducati, "Single-step resection and reconstruction using patient-specific implants in the treatment of benign cranio-orbital tumors," J Oral Maxillofac Surg, vol. 71, issue 11, pp.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.006

1969-1982, November, 2013.

[54] ML. Goodson, D. Farr, D. Keith, RJ. Banks, "Use of two-piece polyetheretherketone [PEEK] implants in orbito zygomatic reconstruction," Br J Oral Maxillofac Surg, vol. 50, issue 3, pp. 268-269, April, 2012.

[55] MA. Zain, MM. Hakam, AH, Abo El Fotouh, "Validity of Peek Patient Specific Implant [PSI] Containing Autogenous Bone Graft for Maxillary Reconstruction Following Lesion Enucleation-A Pilot study," Adv Dent J, vol. 1, issue 1, pp. 21-26, April, 2019.

[56] M. Mounir, M. Shalash, S. Mounir, Y. Nassar, O. El Khatib, "Assessment of three-dimensional bone augmentation of severely atrophied maxillary alveolar ridges using prebent titanium mesh vs customized poly-ether-ether-ketone [PEEK] mesh: A randomized clinical trial," Clin Implant Dent Relat Res, vol. 21, issue 5, pp. 960-967, October, 2019.

[57] H. El-Hawary, M. Mounir, S. Mounir, A. Gibaly, "Primary reconstruction of resected proximal mandibular segments: a novel protocol using patient-specific poly ether-ether ketone [peek] condylar replicas," Egyptian J Oral Maxillofac Surg, vol. 10, issue 2, pp. 77-84, April, 2019.

[58] X. Lin, X. Xiao, Y. Wang, C . Gu, C. Wang, J. Chen, et al., "Biocompatibility of Bespoke 3D-Printed Titanium Alloy Plates for Treating Acetabular Fractures," Biomed Res Int, vol.69, pp. 163-168, February, 2018.

[59] M. Berrone, C. Aldiano, M. Pentenero, S. Berrone, "Correction of a mandibular asymmetry after fibula reconstruction using a custom-made polyetheretherketone [PEEK] onlay after implant supported occlusal rehabilitation," Acta Otorhinolaryngol Ital, vol. 35, issue 4, pp. 285-288, October, 2015.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.015

June 2022
Volume 2
Issue 1

Blood Oxygen Level with Long-Term Use of N95 Face Mask in Dental Practice during Coronavirus Pandemic "Covid-19"

Amr Bayoumi[1], Maha Shawki[2], Amro Abdulaziz[3], Mohammed Allam[3] and Mohamed Mosleh[4]

[1]Professor of Oral and Maxillofacial Surgery, Faculty of Dentistry, King Abdulaziz University, Jeddah, KSA and Alexandria University, Alexandria, Egypt.
[2]Professor of Oral and Maxillofacial Surgery, Faculty of Dentistry, King Abdulaziz University, Jeddah, KSA and Cairo University, Cairo, Egypt.
[3]General practitioner at Faculty of Dentistry, King Abdulaziz University, Jeddah, KSA.
[4]Assistant professor of Oral and Maxillofacial Surgery, Faculty of Dentistry, Beni-Suef University, Beni-Suef, Egypt.

Email: mobayme@kau.edu.sa, mmokhaimar@kau.edu.sa, Amro_Abdulaziz@hotmail.com Mohammed.f.allam@gmail.com, mohamed_mosle7@hotmail.com

Received on, 13 April 2022 - Accepted on, 30 May 2022 - Published on, 28 July 2022

Abstract:

Wearing a mask for a long time, particularly N95, is sometimes uncomfortable, annoying, and confining, making catching breath difficult and reducing the oxygen level in the blood. The study aimed to investigate the change in blood oxygen level when wearing an N95 mask for three hours among dental practitioners in dental clinics and the impact of low O2 levels on the general status of students while working in a stressful environment.

Material and methods: *The sample included 82 adult healthy senior dental students attending the student oral surgery clinical sessions. All Participants had their oxygen saturation SpO2 measured using a portable pulse oximeter before, 1 hour, 2 hours, and 3 hours after wearing the mask, and were allowed to describe their feeling of discomfort throughout the study. Systolic and diastolic blood pressure (SBP and DBP), and heart rate (HR) were also measured before and 3 hours after wearing the mask.*

Results: *84.15% (n= 69) of the participants reported some discomfort affecting their general status and clinical performance. There was a statistically significant increase in mean heart rate after three hours (P-value = 0.001) while there was no statistically significant change in mean systolic/diastolic blood pressure after three hours (P-value = 0.630) and (P-value=0.407), respectively. On the other hand, the mean oxygen saturation after three hours showed a statistically significant lower value compared with baseline measurement.*

Conclusion: *This study revealed a decrease in the oxygen saturation (SpO2) and a slight increase in pulse rate compared to baseline values in all students three hours after wearing an N95 face mask. In addition, the N95 mask induced discomfort in breathing, a decrease in physical performance, and increased fatigue not related to prolonged standing and stress.*

Key words: *Covid-19 pandemic, Dental students, N95 face mask, and oxygen saturation*

Introduction :

Wearing protective equipment became a standard practice to prevent the spread of infection and transmission of disease responsible for coronavirus pandemic. The use of face masks conveys that noncompliance may result from a significant physiologic burden. Due to covid-19 pandemic, usage of medical N95 face masks became a must for healthcare providers.

N95 masks have relatively limited scientific data on their physiologic effects on the user. Having to wear N95 masks for long periods can be uncomfortable for dental professionals because it can trap heat and moisture beneath the mask, leading to exhaustion and fatigue due to difficulty and resistance to breathing while treating complicated cases. They are concerned that this will impact their productivity and level of performance. However, given that the usage of handpieces during routine surgical procedures generates aerosols, it is crucial to consider safety measures to maintain a healthy environment for both the students and the patients.

Recently, concerns have been raised about the safety of wearing face masks in community settings [1]. However, there continues to be controversy over nonmedical mask-wearing. Scheid et al. [2] reported that wearing masks even for an extended period does not produce any clinically relevant changes in circulating oxygen (O2) or carbon dioxide (CO2) concentrations and is not affecting the tidal volume or respiratory rate. However, they did report that wearing a mask causes a modest increase in breathing difficulty due to the mask material filtering particles in the air and moisture retained in the mask material. Furthermore, a study conducted on a convenience sample of 15 house staff physicians

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.015

without lung conditions and 15 veterans with severe chronic obstructive pulmonary disease (COPD) found no major changes in end-tidal carbon dioxide (ETCO2) or oxygen saturation (SpO2) of clinical significance at any time point in either group at rest [3]. These findings demonstrate that wearing a surgical mask has no effect on gas exchange, even in participants with severe lung impairment, and refute suggestions that wearing face masks in public places is dangerous.

On the other hand, ventilation, cardiopulmonary exercise capacity, and comfort were found in a further study [4] to be reduced by surgical masks and highly impaired by FFP2/N95 face masks in healthy individuals. These data can be used to recommend wearing face masks at work or during physical exercise. It was concluded that medical face masks have a marked negative impact on the cardiopulmonary capacity that significantly impairs strenuous physical and occupational activities. In a medical setting, Beder et al. [5] in 2020 conducted an observational study which was carried out amongst 52 surgeons wearing surgical masks, and found a decrease in arterial O2 saturation from approximately 98% before surgery to 96% after surgery which ranged from 1- 4 hours in length. In their study, they reported that pulse rates of the surgeons slightly increased and SPO2 decreased after the first hour which was attributed to either the facial mask or the operational stress. The decrease was more prominent in the surgeons aged over 35 years.

Prolonged use of N95 and surgical masks by healthcare professionals during Covid-19 has shown adverse effects such as headaches, rash, acne, skin breakdown, and impaired cognition [6 -10].

In a recent cross-sectional study looking at the effects of prolonged usage of N95 respirators and surgical masks in healthcare workers 488 experienced generalized nasal discomfort, 303 dry nose, 261 burning sensations in the nose, about 520 developed itchy nose, 560 acne in the face, 390 experienced redness on the face, 676 developed excessive sweating around the mouth, and 582 reported trouble breathing on exertion which is probably due to the mask tightness causing a hypoxic field that leads to physiological changes such as cardiorespiratory stress and metabolic shift [6]. Accordingly, frequent breaks improved hydration and rest skincare and newly designed more comfortable masks were recommended for future management of adverse effects related to prolonged mask use [3, 8]. In a recent study, Scarano et al. [11] reported that wearing a surgical mask for an extended period induces a reduction in circulating O2 concentrations without clinical relevance while an increase in heart rate, shortness of breath, lightheadedness, and headaches were recorded.

The effect of wearing an N95 face mask for a long time on dental students in clinical sessions has not been yet reported. Only one study by Gaikwad et al. [12] was published in 2021 in which a total of 90 exam-going dental students were included who were instructed to wear N95 masks for 4 hours. It was concluded that respiratory consequences due to the reduction in blood oxygen saturation level can be harmful. Blood oxygenation plays an essential role in providing the muscles, brain, and other organs the energy they need to function properly normal. The normal pulse oximeter readings in the healthy people range from 95% to 100%. Values under 90% are considered critical and indicate the need for supplemental oxygen. This condition is known as hypoxemia and its symptoms include severe breathing difficulty, increased heart rate, and chest tightness and pain. A pulse oximeter can quickly measure the oxygen saturation of hemoglobin accurately and in a reliable way. Pulse oximetry is a noninvasive method to measure blood oxygen saturation continuously. Pulse oximetry has a high sensitivity of 92% and a specificity of 90% when detecting hypoxia at a threshold of 92% oxygen saturation [13]. There is no set standard of oxygen saturation where hypoxemia occurs. The generally accepted standard is that a normal resting oxygen saturation of less than 95 is considered abnormal [13].

Aim of the work

This study aims to evaluate whether blood oxygen saturation level is affected by wearing an N95 mask among dental students for 3 hours. The primary focus of this study was to measure the student's oxygen saturation status and discomfort while they were engaged in their daily routine activities in the oral surgery clinics.

Materials and Methods

This prospective crossover observational study is conducted in an oral surgery clinical session over the period from May 2021 to June 2021. The study was approved by the local research ethics committee no. 2210221 following the declaration of Helsinki guidelines. 82 senior dental students were included in this study. Participation was voluntary and participants were prospectively recruited and approached to obtain informed verbal consent to participate in the study. Students eligible for inclusion were senior healthy students aged between 22-25 years, free from any medical condition that makes breathing difficult, and who wore the N95 mask continuously for three hours. Before enrollment the researchers excluded participants who interrupted the three-hour continuous period and subjects who had comorbid cardiac or respiratory conditions that could lead to dyspnea or hypoxia such as chronic respiratory diseases (COPD), chronic lung diseases, asthma, sleep apnea, anemia, hypertension, diabetes, smokers, and those who voluntarily quit the study to minimize variability.

The researchers provided participants with disposable sterile valveless N95 face masks and instructions on how to correctly wear the mask to ensure adequate nose and mouth coverage and to remove it with proper sanitization handling technique. Data concerning medical history were recorded by interviewing the participants preoperatively by two registered interns who were responsible for data collection. All participants had their peripheral oxygen saturation SpO2 measured using a portable pulse oximeter before wearing the mask baseline, 1 hour, 2 hours, and 3 hours after wearing the mask. At the end of the session, while they are performing the usual daily patient care including

simple and complicated teeth extraction, and a surgical dental procedure under staff supervision, blood oxygen saturation was measured using the same pulse oximeter with the probe applied to the second finger of the right hand. Participants were allowed to describe their feeling of discomfort if any throughout the study systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) were also measured on the same day before and 3 hours after wearing the mask. Data obtained were compiled on a Microsoft office excel sheet and were subjected to statistical analysis, numerical data were explored for normality by checking the distribution of data and using normality tests of Kolmogorov, Smirnov, and Shapiro-Wilk tests. All data showed normal parametric distribution. Data were presented as mean, standard deviation (SD), and 95% confidence interval (95% CI) for the mean difference values. Paired t-test was used for comparisons related to heart rate and blood pressure. Repeated measures ANOVA test was used for comparisons related to oxygen saturation. Bonferroni's posthoc test was used for pairwise comparisons when the ANOVA test is significant. The level of significance was set at $p \leq 005$. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Results

1) Baseline demographic data

The present study was conducted on 82 subjects: 23 females (28%) and 59 males (72%) and the mean and standard deviation values for age were 23.5 (±1.3) years old with a minimum of 22 and a maximum of 25 years old. The mean and standard deviation values for weight were 76.1 (±17.1) kilograms with a minimum of 44 and a maximum of 120 kilograms. The mean and standard deviation values for height were 1.71 (±0.09) meters with a minimum of 1.53 and a maximum of 1.88 meters.

2) Medical history and feeling of discomfort

All the participants included in this study were medically free. The follow-up rate was 100%. Most of the participants 84.15% (n= 69), apart from the physiologic and biological effect of the mask usage, reported some discomfort in terms of difficult breathing, quick exhaustion, tiredness, hotness, and slow performance not related to prolonged standing and stress.

3) Heart rate (beats/min.)

When preoperational and post-operational pulse rates were compared there was a statistically significant increase in mean heart rate after three hours (P-value = 0.001, Effect size = 0.311). Table I, Fig. 1.

Table I: Descriptive Statistics and Results of Paired t-test for Comparison between Heart Rate at Baseline and after Three Hours of Wearing a Mask

Baseline	3 hours	95% CI for the difference	*P*-value	*Effect size (d)*
Mean (SD)	Mean (SD)			
82.83 (10.85)	85.96 (8.64)	-4.85 - -1.41	0.001*	0.311

*: Significant at $P \leq 0.05$

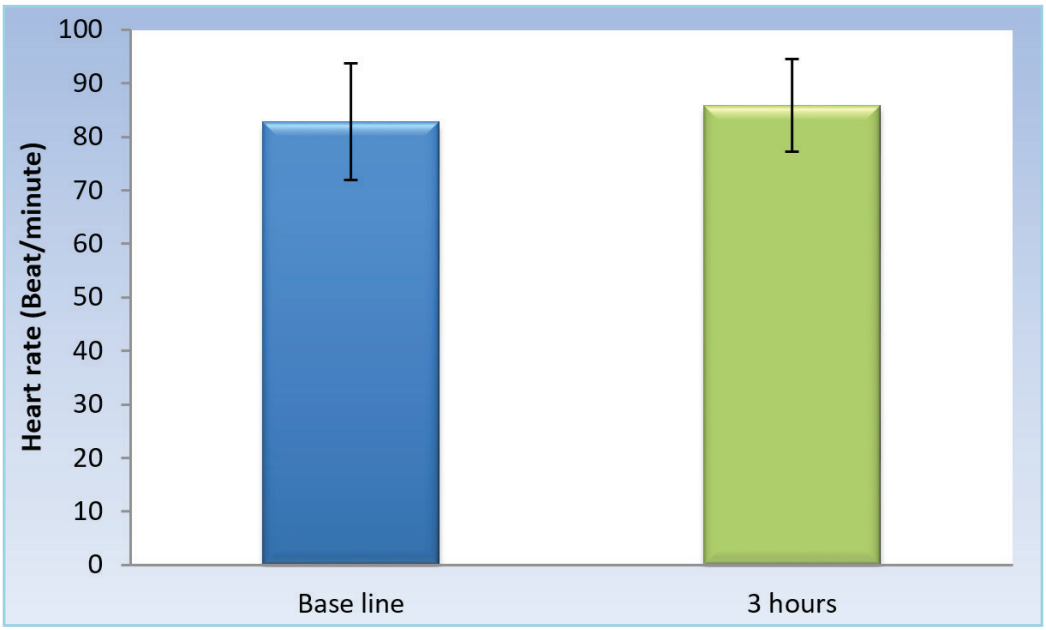


Fig. 1. Bar chart representing mean and standard deviation values for heart rate at baseline and after three hours.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.015

4) Blood pressure (mmHg)

There was no statistically significant change in mean systolic/diastolic blood pressure after three hours (P-value = 0.630, Effect size = 0.066) and (P-value = 0.407, Effect size = 0.108), respectively. Table II, Fig. 2.

Table II: Descriptive Statistics and Results of Paired t-test for Comparison between Blood Pressure at Baseline and after Three Hours of Wearing a Mask

Blood pressure	Baseline Mean (SD)	3 hours Mean (SD)	95% CI for the difference	*P*-value	*Effect size (d)*
Systolic	116.43 (3.49)	116.2 (3.57)	-0.72 – 1.19	0.630	0.066
Diastolic	75.8 (3.86)	76.22 (3.84)	-1.4 – 0.57	0.407	0.108

**: Significant at P ≤ 0.05*

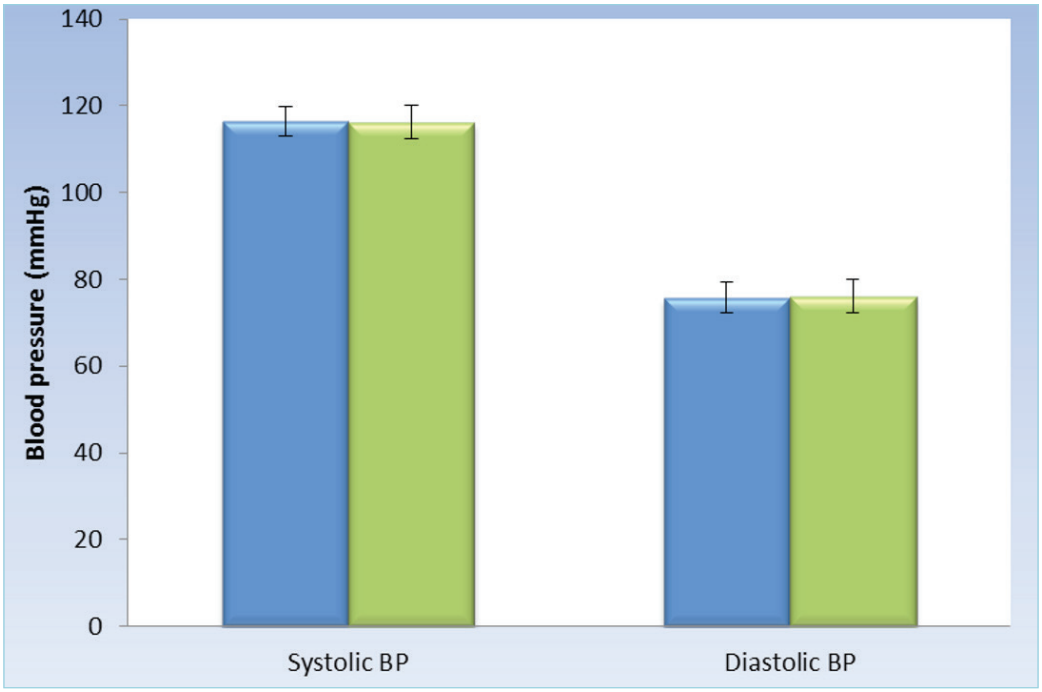


Fig. 2. Bar chart representing mean and standard deviation values for blood pressure at baseline and after three hours.

5) Oxygen saturation (%)

When the values for oxygen saturation of hemoglobin were compared, there was a statistically significant change in mean oxygen saturation by time (P-value <0.001, Effect size = 0.532). There were statistically significant differences only between pre-and post-operational values from baseline to 1 hour and from 1 to 2 hours. Pairwise comparisons using Bonferroni's posthoc test revealed a statistically significant decrease in mean oxygen saturation after one hour as well as from one to two hours followed by a non-statistically significant change in oxygen saturation from two to three hours Table III, Fig. 3. The mean oxygen saturation after three hours showed a statistically significant lower value compared with baseline measurement. Table IV shows a comparison of the mean change of SPO2 values of students before and after wearing the N95 mask at 1, 2 and 3 hours.

Table III: Descriptive Statistics and Results of Repeated Measures ANOVA Test for Comparison between Oxygen Saturation at Baseline, after One, Two as well as Three Hours of Wearing a Mask

Time	Mean (SD)	95% CI for the difference	*P*-value	*Effect size (Partial Eta Squared)*
Base line	98.61 (0.68) [A]	Base line vs. 1 h: -0.87 – -0.15	<0.001*	0.532
1 hour	98.1 (1.05) [B]	Baseline vs. 2 h: -1.81 – -0.82		
2 hours	97.29 (1.58) [C]	Baseline vs. 3 h: -2.08 – -1.07		
3 hours	97.04 (1.67) [C]	1 h vs. 2 h: -1.39 – -0.22		
		1 h vs. 3 h: -1.63 – -0.5		
		2 h vs. 3 h: -0.8 – 0.29		

**: Significant at P ≤ 0.05, Different superscripts are statistically significantly different*

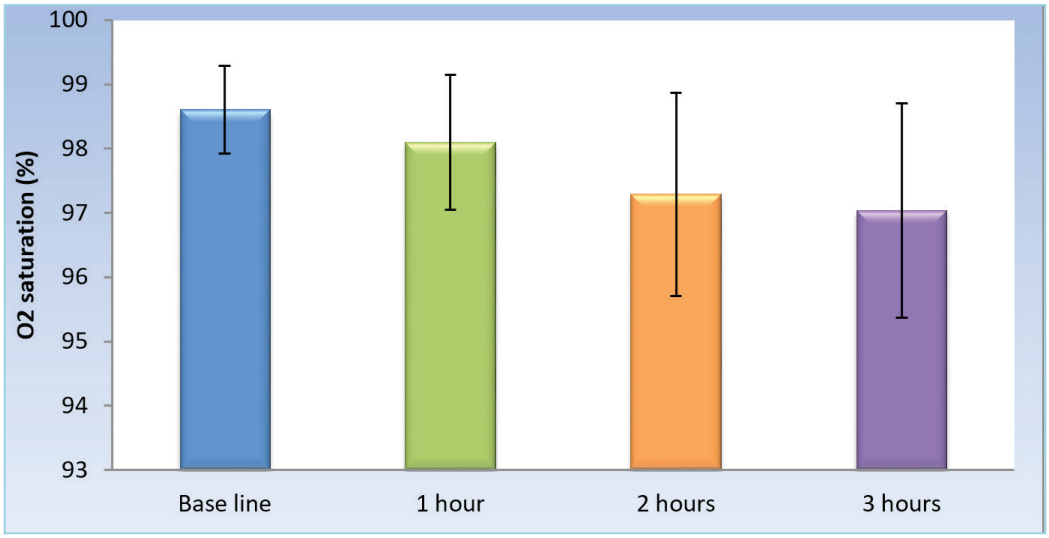


Fig. 3. Bar chart representing mean and standard deviation values for oxygen saturation at baseline, after one, two as well as three hours.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2022.02.1.015

Table IV: Descriptive Statistics for the Amounts of Change in Oxygen Saturation after Wearing a Mask

Time	Mean change	95% CI for the change
Baseline vs. 1 h	-0.51	-0.87 – -0.15
Baseline vs. 2 h	-1.32	-1.81 – -0.82
Baseline vs. 3 h	-1.57	-2.08 – -1.07
1 h vs. 2 h	-0.81	-1.39 – -0.22
1 h vs. 3 h	-1.06	-1.63 – -0.5
2 h vs. 3 h	-0.26	-0.8 – 0.29

Discussion

There has been no controlled study concerning the effect of N95 masks on the level of blood oxygenation in students during their daily dental practice. Oral surgery providers operating face to face with the patients are at high risk of catching respiratory infections [14]. In this study, the researchers included only those working in an oral surgery session to grab those with a high level of physical activity while wearing the N95 mask. In this study, they measured the systolic and diastolic blood pressure and pulse rate before and 3 hours after wearing the mask. Results revealed a statistically significant increase in pulse rate (from 82.83 to 85.96 bpm) and unchanged blood pressure after 3 hours. Sometimes, the combination of low or unchanged blood pressure and high pulse rate signifies that the body is not getting enough oxygen, and heart rate can increase without any change in blood pressure.

As the heart beats became faster healthy blood vessels will dilate in size to allow increased blood flow, particularly in young healthy individuals which helps the blood pressure remain relatively stable [13].
Oxygen saturation SPO2 was measured by a pulse oximeter and showed a statistically significant decrease in the mean blood O2 saturation level of the student from 98.61% to 97.04%, after three hours, not pertinent to prolonged standing or stress as the discomfort occurred both in simple and long surgical dental procedures. These results coincide with further studies by Beder et al. [5] and Scarano et al. [11].

In this study, although there are minimal psychological impacts, however, some studies [15–18] showed theoretical evidence suggesting that there may be consequential impacts of mask-wearing on the basic psychological needs of competence autonomy, and relatedness. These psychological impacts may contribute to the controversy associated with wearing masks during the covid-19 pandemic [2]. Scarano et al. [19] in 2021 detailed that the dental specialists who wear individual defensive gear during oral medical procedures often experience exhaustion, actual distress, and conceivably even disintegration of careful judgment and execution, despite the presence of standard cooling in the working rooms. They added that an increase in airflow resistance, facial skin temperature, and physical discomfort during wearing masks can induce them to move it, with an increased risk of contagion. In this study, students were not allowed to wear the masks improperly or remove them from their faces.

Considering students' discomfort, it has been suggested that the facial temperature augmentation discomfort is also caused by exhaled CO2 levels under the protective facial mask, with sweating and hot flashes.

This could attribute to the difficult breathing, quick exhaustion, tiredness, hotness, and slow performance the students had experienced. Results of this study will help the researchers set standardized decisions and recommendations with the best evidence-based practice to assist in understanding human factors, recently acknowledged as an essential part of patient safety. In addition to developing guidelines on how long students should wear the N95 mask to promote their safety and maintain a safe clinical working environment by looking after their health and provide a safe practice and healthcare delivery processes. According to the findings, intermittent usage of the face mask (time off), work breaks and shifts, and rest are recommended to allow for proper breathing, improved hydration, and future management of adverse effects related to prolonged use of masks. The major limitation of this study was the inability to assess the effects of N95 mask usage over longer durations added that the sample size for the study was small, thus future research is encouraged with larger sample size. Furtherly, the researchers did not compare N95 mask effect to the regular surgical mask effect on the students as the researchers did not have a comparison arm.

Conclusion

This study revealed a decrease in the oxygen saturation (SpO2) and a slight increase in pulse rate compared to baseline values in all students three hours after wearing an N95 face mask. In addition, N95 mask induces discomfort in breathing, a decrease in physical performance, and increased fatigue not related to prolonged standing and stress.

Conflicts of interest: The authors declared no potential conflicts of interest.

Declarations of trial registration for observational studies and randomized controlled trials ethics. Approval: The study was approved by the local research ethics committee no. 2210221 following the declaration of Helsinki guidelines data availability all the data are available when needed.

Consent for publication: All the authors are pleased to submit the attached manuscript entitled blood oxygen level with long-term use of N95 face mask in dental practice during covid-19 pandemic to be considered for publication in (Advances in Medical, Pharmaceutical and Dental research)

Funding sources: None are declared
Acknowledgments: None are declared

References

[1] Chan NC, Li K, Hirsh J, "Peripheral Oxygen Saturation in Older Persons Wearing Nonmedical Face Masks in Community Settings," JAMA Research letters [Online]. October 30 2020. Available: https://jamanetwork.com/journals/jama/fullarticle/2772655.

[2] J. Scheid, S. Lupien, G. Ford, S. West, "Commentary Physiological and Psychological Impact of Face Mask Usage during the COVID-19 Pandemic," Int. J Environ Res Public Health, vol. 17 issue 18, p. 6655, Sep. 2020.

[3] R. Samannan, G. Holt, R. Candelario, M. Mirsaeidi, M. Campos, "Effect of Face Masks on Gas Exchange in Healthy Persons and Patients with Chronic Obstructive Pulmonary Disease" Ann Am Thorac Soc, vol. 18, issue 3, pp. 541-544, March 2021.

[4] S. Fikenzer, T. Uhe, D. Lavall, U. Rudolph, et al., "Effects of surgical and FFP2/N95 face masks on cardiopulmonary exercise capacity" Clin Res Cardiol, vol.102, issue 12, pp.1522-1530, Dec. 2020.

[5] A. Beder, Ü . Büyükkoçak, H. Sabuncuoğlu, ZA. Keskil, S. Keskil, "Preliminary report on surgical mask induced deoxygenation during major surgery," Neurocirugia (Astur), vol. 19, issue 2, pp. 121-126, April 2008.

[6] T. Rebmann, R. Carrico, J. Wang, "Physiologic and other effects and compliance with long-term respirator use among medical intensive care unit nurses" Am J Infect Control, vol. 41, issue 12, pp.1218-1223, Dec. 2013.

[7] World Health Organization, "Mask use in the context of COVID-19: interim guidance," Document [Online], December 1 2020. Available: https://apps.who.int/iris/handle/10665/337199. License: CC BY-NC-SA 3.0 IGO

[8] L. Matusiak, M. Szepietowska, P. Krajewski, et al., "Inconveniences due to the use of face masks during the COVID-19 pandemic: a survey study of 876 young people," Dermatol Ther, vol. 33, issue 4, p. e13567, July 2020.

[9] Ong, J, Bharatendu, C, Goh Y, Tang, J, Sooi, K, Tan Y L, Tan, B, Teoh, HL, Ong S T, Allen DM, SharmaV K, "Headaches Associated With Personal Protective Equipment - A Cross-Sectional Study Among Frontline Healthcare Workers During COVID-19," Headache, vol. 60, issue 5, pp. 864-877, May 2020.

[10] E. Rosner, "Adverse Effects of Prolonged Mask Use among Healthcare Professionals during COVID-19," J Infect Dis Epidemiol, vol. 6, issue 3, pp. 130-135, June 2020.

[11] A. Scarano, F. Inchingolo, B. Rapone, et al. "Protective Face Masks: Effect on the Oxygenation and Heart Rate Status of Oral Surgeons during Surgery," Int. J. Environ. Res. Public Health, vol.18, issue 5, pp. 2363-367, February 2021.

[12] R. Gaikwad, A. Banodkar, V. Nandgaonkar, L. Fernandes, et al., "Respiratory Consequences of N95 Mask during Covid-19 Pandemic- An Observational Study," International Journal of Health Sciences and Research, vol.11, issue 4, pp. 407-411, April 2021.

[13] W. Lee, K. Mayberry, R. Crapo, R. Jensen, "The accuracy of pulse oximetry in the emergency department," Am J Emerg Med, vol. 18, issue 4, pp. 427-31, Jul 2000.

[14] I. Bordea, E. Xhajanka, S. Candrea, S. Bran, et al., "Coronavirus (SARS-CoV-2) Pandemic: Future Challenges for Dental Practitioners," Microorganisms, vol. 8, issue 11, pp. 704- 1708. October 2020.

[15] E. Lim, R. Seet, K. Lee, et al., "Headaches and the N95 face-mask amongst healthcare providers," Acta Neurol Scand, vol. 113, issue 3, pp. 199-202, March 2006.

[16] L. Nickell, E. Crighton, C. Tracy, et al., "Psychosocial effects of SARS on hospital staff: a survey of a large tertiary care institution," CMAJ, vol. 170, issue 5, pp. 793-798, March 2004.

[17] J. Zhu, S. Lee, D. Wang, H. Lee, "Effects of long-duration wearing of N95 respirator and surgical facemask: a pilot study. g-duration wearing of N95 respirator and surgical facemask: a pilot study," J Lung Pulm Respir Res, vol. 1, issue 4, pp. 97-100, November 2014.

[18] Y. Li, H. Tokura, et al., "Effects of wearing N95 and surgical facemasks on heart rate, thermal stress, and subjective sensations," Int Arch Occup Environ Health, vol. 76, issue 6, pp. 501-509, Jul 2005.

[19] A. Scarano, F. Inchingolo, F. Lorusso, "Facial Skin Temperature and Discomfort When Wearing Protective Face Masks: Thermal Infrared Imaging Evaluation and Hands Moving the Mask," Int J Environ Res Public Health. Vol. 17, issue 13, p. 4624, June 2020.

AMPDR

Advances in Medical, Pharmaceutical and Dental Research Journal

ACADEMY Publishing Center

Volume 2, Issue 1, June 2022 - ISSN 2812-4898