СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted*

ISSN Online 2406-0895

Current Topic / Актуелна тема

Vesna Stevanović[1,2,♣], Gordana Kovačević[1,2], Marina Boboš[3], Predrag Stevanović[2,3]

Vaccination – a dilemma for a pediatric anesthesiologist: When is the right moment?

Вакцинација – дилема за педијатријског анестезиолога: када је прави тренутак?

[1]Dr Vukan Čupić Mother and Child Health Care Institute of Serbia, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Dr Dragiša Mišović – Dedinje Clinical Hospital Center, Belgrade, Serbia

Received: February 23, 2023
Revised: November 6, 2023
Accepted: November 21, 2023
Online First: November 23, 2023
DOI: https://doi.org/10.2298/SARH230223111S

♣**Correspondence to:**
Vesna STEVANOVIĆ
Dr Vukan Čupić Mother and Child Health Care Institute of Serbia, Radoja Dakića 6–8, 11070 Belgrade, Serbia
E-mail: **vesna.stevanovic@med.bg.ac.rs**

Vaccination – a dilemma for a pediatric anesthesiologist: When is the right moment?

Вакцинација – дилема за педијатријског анестезиолога: када је прави тренутак?

SUMMARY
Possible immune system interactions due to vaccination and drugs used in general anesthesia represent a dilemma for pediatric anesthesiologists in everyday practice. Immunosuppression caused by anesthesia and surgical trauma can affect the immunization process and cause-specific unwanted reactions. On the other hand, side effects due to vaccination can confuse clinicians in the immediate postoperative course. Both the nature of the vaccine and the type of surgery determines the delay period of elective surgical intervention. This current topic aims to present the scientific facts about the complex interactions between vaccination, immunization, general anesthesia, and surgical trauma and to provide recommendations for preoperative preparation.
Keywords: anesthesia; children; immunization; vaccines

САЖЕТАК
Могуће интеракције имуног система због вакцинације и лекова који се користе у општој анестезији представљају дилему за педијатријског анестезиолога у свакодневном раду. Имуносупресија изазвана процесом анестезије и хируршком траумом може утицати на вакцинални одговор организма и изазвати одређене нежељене реакције. С друге стране нуспојаве због вакцинације могу збунити клиничаре у непосредном постоперативном току. Природа вакцине и врста оперативног захвата одређују период одлагања елективне хирурушке интервенције. Циљ ове актуелне теме је да предочи научне чињенице о комплексним интеракцијама између вакцинације, имунизације, опште анестезије и хируршке трауме и да пружи важеће смернице за преоперативну припрему.
Кључне речи: анестезија; деца; имунизација; вакцине

INTRODUCTION

Vaccination causes the host's desired and controlled immune response to prevent the development of certain diseases and their complications. The schedule of mandatory vaccinations is most frequent in childhood [1]. At the same time, in children of all ages, there is sometimes necessary to perform a surgical intervention under anesthesia. Medicines and complex anesthesia processes also cause specific immunomodulatory functions and tissue trauma caused by surgery [2]. The vaccine is known to cause side effects similar to the stress response after surgery [3, 4]. On the other hand, scientists are trying to determine if the impact of the anesthetics changes the vaccine's effectiveness. That is why there are still preoperative dilemmas among pediatricians, anesthesiologists and surgeons: whether and when to vaccinate a child before surgical intervention, whether to postpone surgery because of vaccination and when it is safe to continue with regular vaccinations after surgery.

The recommendations of the World Association of Pediatric Anesthesiologists differ regarding the delay of surgery when it comes to live attenuated vaccines [5]. The consensus was made for inactivated vaccines. Interestingly, in recent years, the possibility of

intraoperative administration of influenza and pneumococcal vaccines to specific pediatric patients during general anesthesia further complicates the abovementioned dilemmas [6].

FACTS ABOUT IMMUNIZATION

Immunization of the organism is carried out actively and passively. The active method involves using vaccines against a specific infectious disease, and the passive process involves using a defined immunoglobulin, antibody or serum. Currently, there are about 20 vaccines with which people can be immunized. The World Health Organization estimates this revolutionary medical discovery saves 3.5 to 5 million lives yearly [7]. It has been scientifically confirmed that individual variations in the strength of the immune response can have consequences on the protective efficiency and length of protection of the organism against a particular infectious disease. Factors affecting individual immunization variations are gender, genetics, comorbidities, and age-related factors [8, 9]. External factors include infections, antibiotics, probiotics and previous vaccinations.

Habits such as smoking, alcohol use, stress, sleep quality, nutritional status and exposure to toxins contribute to these complex processes. The most crucial factor in forming immunity is the vaccine itself (type of vaccine, dose, vaccination calendar, site of application, route of administration and co-administration of vaccines) [10]. Administration of drugs at the time of vaccination raises the question of vaccine effectiveness. These can be drugs the patient takes due to a chronic disease, but also analgesics and antipyretics that are recommended due to the side effects of vaccines [11]. In daily clinical work, pediatric anesthesiologists face preoperative dilemmas as to whether anesthesia drugs, the anesthesia process, and surgical trauma affect the immunization process in the body in the case of vaccination and vice versa. It is estimated that a sixth of operated children are at the age when, according to the national schedule, it is necessary to give the vaccine [12]. The most significant number of postponements of elective surgeries occurs at the age of up to 6 months of life. The solution to this problem is better coordination and harmonization of positions on the issue of vaccinations between pediatricians, surgeons and anesthesiologists. An individual approach to the patient is recommended.

FACTS ABOUT ANESTHESIA AND IMMUNE RESPONSE

It has been scientifically proven that surgical intervention and general anesthesia cause a disturbance in the activity of the immune system. There are several explanations for this statement: the stress response with the release of catecholamines and cortisol suppresses macrophage function, phagocytic activity of leukocytes, phagocytic mobilization, complement fixation, lymphocyte transformation, T cell activity and antibody formation 4 to 12 days after surgery. It has been proven that anesthetic drugs are immunomodulators. Intraoperative events such as pain, hypoperfusion, hypothermia, hyperglycemia, transfusion or extracorporeal circulation also have an immunosuppressive effect. At the same time, there is an increased production of proinflammatory cytokines [13]. The degree of immunosuppression depends on the extent of the stress response, surgical trauma, perioperative pain therapy and infection. An immunocompetent child usually has no clinical manifestations of laboratory signs of transient immunosuppression due to anesthetic effects. Drugs for anesthesia have an immunomodulatory effect by changing the components of humoral and cellular immunity. Volatile anesthetics (halothane, sevoflurane, isoflurane, enflurane) inhibit the production of proinflammatory cytokines, the proliferation of lymphocytes, the activity of neutrophils and natural killer cells, and the generation of free oxygen radicals while they do not affect the function of B lymphocytes. This condition can last for several days after exposure to volatile anesthetics. Nitrous oxide gas inhibits the activity of monocytes to the extent that it does not increase the risk of infection after surgery. A similar effect is shown by midazolam, ketamine and fentanyl [14, 15, 16]. Thiopentone sodium reduces lymphocyte production and natural killer (NK) cell function. Propofol inhibits neutrophils, macrophages and monocytes and increases infiltration of the operative wound by NK cells and helper T cells [17]. With its immunosuppressive effect, propofol does not affect the humoral immunity components. The benzodiazepines (lorazepam) show a more significant impact on the innate immune response. Studies have shown that dexmedetomidine and clonidine do not affect neutrophil function [18].

Opioids have a suppressive effect on the immune system, especially morphine and fentanyl, in contrast to alfentanyl, remifentanyl and sufentanyl. Unlike opioids, tramadol has a stimulating effect on NK cells [19]. Local anesthetics blocking sympathetic activity do not show an immunosuppressive effect [15, 17]. Transient neutropenia and lymphopenia are most often registered after surgical intervention and general anesthesia in children [20]. Clinical manifestations of the stress response after surgery are mild in the form of agitation and restlessness, elevated temperature, rash, pain, and rarely inflammation and sepsis. However,

some works assume that the influence on the immune response due to anesthesia could increase the susceptibility to infection and even the spread of malignant tumors [21]. Cases of reactions after anesthesia in recently vaccinated children in the form of intussusception (after rotavirus vaccine), hypotonic crisis (after diphtheria, pertussis, and tetanus vaccine) and spread of infection in surgically immunocompromised patients originating from the live attenuated vaccine (oral polio vaccine, which is genetically unstable) have been described [22]. On the other hand, there is a justified fear that anesthetic drugs will change the immune effect of the vaccine if the anesthetics have already caused a certain degree of immunosuppression. Human studies have shown that the production of antibodies to anti-tetanus toxoids is lower if the child has been exposed to general anesthesia and surgery [23].

Also, fever, soreness at the application site, coryza, tearfulness, vomiting and malaise can be attributed to vaccination and surgical stress, which can confuse the clinician. Usually, these symptoms appear in the first 24-48 hours after vaccination, with the inactive form in 20% of vaccinated children and up to three weeks after the live attenuated vaccine (in 6% of cases and after the first dose of the vaccine). There are rare forms of severe post-vaccination complications, such as mumps meningitis (incidence 1:300,000 in vaccinated children) [24].

RECOMMENDATIONS OF THE WORLD ASSOCIATIONS OF PEDIATRIC ANESTHESIOLOGISTS

World Associations of Pediatric Anesthesiologists recommend delaying elective surgery one week after the inactivated vaccine and three weeks after the live attenuated vaccine (measles, mumps, and rubella vaccine - MMR, oral polio, tuberculosis vaccine) [23]. The Association of Pediatric Anesthesiologists and Intensivists of Serbia has the same attitude [1]. Recent research has influenced the Association of Pediatric Anesthesiologists of Great Britain and Ireland since 2021. advises postponing elective surgery 48 hours after administration of an inactivated vaccine (DTP, Haemophilus influenzae type B vaccine - Hib, meningitis type C, poliovirus). At the same time, they do not recommend postponing live attenuated vaccines surgical interventions (provided that the child is in good health) [25]. After oral vaccination with the live attenuated poliovirus, elective surgery should be postponed for 30 days [26]. The planned vaccination should be delayed for at least seven days if the patient had general anesthesia and surgery. However, if the child received blood or blood derivatives during surgery and perioperative treatment, there are special warnings when planning to continue vaccination for MMR and varicella. If the patient received erythrocytes, the interval for

postponing vaccination is up to five months; whole blood - 6 months; immunoglobulins for the treatment of idiopathic thrombocytopenic purpura - 8 to 11 months; plasma or platelets - 7 months; tetanus immunoglobulin - 3 to 5 months; varicella immunoglobulin - 5 months; cytomegalovirus immunoglobulin – 6 months; hepatitis B immunoglobulin – 3 months; normal human immunoglobulin as hepatitis A prophylaxis – 3 months and normal human immunoglobulin as measles prophylaxis – 5 to 6 months [27]. Particular caution is required in children with congenital heart defects after surgical correction and extracorporeal circulation [28]. In these circumstances, the vaccines against measles, mumps, and rubella (the MMR vaccine) and the varicella vaccine are not recommended for the next seven months. If there is a need for low-dose aspirin after cardiac surgery, the aspirin should be continued, and the child should be vaccinated against varicella without delay. If cardio surgery is planned, the child can be vaccinated seven days before the intervention or 4-6 weeks after the surgery. Children after Norwood's operation, especially those born prematurely, are at high risk of vaccination because they may have sudden systemic and peripheral vascular resistance changes as an adverse event. Therefore, these children should be hospitalized after vaccination and observed for 72 hours [29]. If a splenectomy is planned, it is necessary to vaccinate the child at least two weeks before the operation with the meningococcal, pneumococcal and Hib vaccines. Studies in adult patients have shown an enviable growth of antibodies to the mentioned vaccines in the case of urgent splenectomy if the vaccines are given immediately after the operation [30]. Vaccination against influenza and pneumococcus is increasingly encouraged after minor surgical interventions and diagnostic procedures under analgosedation during hospitalization or hospital discharge, especially in uncooperative or developmentally disabled children [12]. If the child is at an age when immunization is frequent (up to 6 months), it is better to postpone elective surgery at that time for older age. There is evidence that any delay in vaccination is harmful because an unvaccinated child is exposed to a high risk of developing an infectious disease, and the collective is at risk of an epidemic. The vaccination dilemma does not exist when it comes to emergency surgical interventions. In the case of co-administration of the vaccine and anesthesia drugs in those circumstances, careful patient monitoring is required for unexpected symptoms, especially after complicated and significant operations and long postoperative recovery. A special request is a vaccine against Severe Acute Respiratory Syndrome Covidvirus19, which is currently not recommended for children aged under 6 months [31]. For now, this vaccine is not given in co-administration with other vaccines. A one-week gap is required between vaccines of different types. Also, a seven-day break is recommended after surgery until the vaccine is administered [25].

CONCLUSION

Vaccination is a revolutionary discovery in medicine that saves millions of lives every year. The reasons for postponing the planned vaccination should be precisely defined and reduced to a minimum. Postponement of vaccination or elective surgery is necessary if they overlap in time because both medical interventions have an immunosuppressive effect. The appearance of side effects in both cases can confuse diagnostic and therapeutic decisions.

Ethics: The manuscript has been written in accordance with the ethical standards of the respective institution and the journal.

Conflict of interest: None declared.

REFERENCES

1. Jovanovski-Srceva M, Stojanoski S, Stevic M, Kuzmanovski I, Simic D.Vaccination and Anaesthesia. In: Simic D, ed. Paediatric Anaesthsiology. Udruženje dečijih Anesteziologa i Intenzivista Srbije, Akademska misao; 2020.p 347-353.
2. Szakmany T. Anesthesia and immunomodulation: from basic science to clinical trials. Minerva Anestesiol. 2020 Feb;86(2):126-128. doi: 10.23736/S0375-9393.19.14327-1. PMID: 32118383.
3. Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how's and what's of vaccine reactogenicity. NPJ Vaccines. 2019 Sep 24;4:39. doi: 10.1038/s41541-019-0132-6. PMID: 31583123; PMCID: PMC6760227.
4. Vaccine Adverse Event Reporting System (VAERS). Center for Disease Control website. July 23, 2020. Accessed July 30. 2020. https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html
5. American Academy of Pediatrics. Vaccination during hospitalization, including anesthesia and surgery. In Kimberlin DW, Brady MT, Jackson MA, Long, SS, eds. Red Book®: 2015 report of the committee on infectious diseases. American Academy of Pediatrics; 2015:98.
6. Navarro RA, Lin CC, Colli B, et al. Safety of Influenza Vaccination During Orthopaedic Surgery Hospitalizations. J Am Acad Orthop Surg. 2022 Jan 15;30(2):e155-e163. DOI: 10.5435/jaaos-d-21-00101. PMID: 34967797.
7. World Health Organisation [homepage on the Internet]. Geneva: Vaccines and Immunization; [cited 2023 Jan 6] Available from: https://www.who.int/health-topics/vaccines-and-immunization/.
8. Walker EJ, MacDonald NE, Islam N, et al. Completeness and timeliness of diphtheria-tetanus-pertussis, measles-mumps-rubella, and polio vaccines in young children with chronic health conditions: A systematic review. Vaccine. 2019 Mar;37(13):1725-1735. DOI: 10.1016/j.vaccine.2019.02.031. Epub 2019 Feb 25. PMID: 30814030
9. Macina D, Evans KE. Pertussis in Individuals with Comorbidities: A Systematic Review. Infect Dis Ther. 2021 Sep;10(3):1141-1170. doi: 10.1007/s40121-021-00465-z. Epub 2021 Jun 12. PMID: 34117998; PMCID: PMC8322178.
10. Zimmermann P, Curtis N. Factors That Influence the Immune Response to Vaccination. Clin Microbiol Rev. 2019 Mar 13;32(2):e00084-18. DOI:10.1128/CMR.00084-18 PMID 30867162
11. Das RR, Panigrahi I, Naik SS. The effect of prophylactic antipyretic administration on post-vaccination adverse reactions and antibody response in children: a systematic review. PLOS One. 2014 Sep 2;9(9):e106629.DOI:10.1371/journal.pone.0106629 PMID:25180516
12. Lin C, Vazquez-Colon C, Geng-Ramos G, Challa C. Implications of anesthesia and vaccination. Paediatr Anaesth. 2021 May;31(5):531-538.DOI: 10.1111/pan.14148. PMID:33540468
13. Rossaint J, Zarbock A. Perioperative Inflammation and Its Modulation by Anesthetics. Anesth Analg. 2018 Mar;126(3):1058-1067.DOI: 10.1213/ANE.0000000000002484. PMID: 28922235
14. Yuki K, Hou L, Shibamura-Fujiogi M, Koutsogiannaki S, Soriano SG. Mechanistic consideration of the effect of perioperative volatile anesthetics on phagocytes. Clin Immunol. 2021 Jan;222:108635. doi: 10.1016/j.clim.2020.108635. Epub 2020 Nov 17. PMID: 33217544; PMCID: PMC7856197.
15. Kurosawa S, Kato M. Anesthetics, immune cells, and immune responses. J Anesth. 2008;22(3):263–77. DOI: 10.1007/s00540-008-0626-2 PMID: 18685933
16. Horiguchi Y, Ohta N, Yamamoto S, Koide M, Fujino Y. Midazolam suppresses the lipopolysaccharide-stimulated immune responses of human macrophages via translocator protein signaling. Int Immunopharmacol. 2019;66:373-382. DOI:10.1016/j.intimp.2018.11.050 PMID: 30530051.
17. Siebert JN, Posfay-Barbe KM, Habre W, Siegrist CA. Influence of anesthesia on immune responses and its effect on vaccination in children: a review of evidence. Paediatr Anaesth. 2007 May;17(5):410-20. DOI: 10.1111/j.1460-9592.2006.02120.x PMID: 17474946.
18. Ackerman RS, Luddy KA, Icard BE, Piñeiro Fernández J, Gatenby RA, Muncey AR. The Effects of Anesthetics and Perioperative Medications on Immune Function: A Narrative Review. Anesth Analg. 2021 Sep 1;133(3):676-689. DOI: 10.1213/ANE.0000000000005607. PMID: 34100781.
19. Kaye AD, Patel N, Bueno FR, Hymel B, Vadivelu N, Kodumudi G, Urman RD. Effect of opiates, anesthetic techniques, and other perioperative factors on surgical cancer patients. Ochsner J. 2014 Summer;14(2):216-28.PMID: 24940132; PMCID: PMC4052589.
20. U.S. Department of Health and Human Services [homepage on the Internet] Washington: Vaccine side effects.[update Apr 28, 2021; accessed Oct 13, 2022]. Available from:https://www.hhs.gov/immunization/basics/safety/side-effects/index.html.
21. Short JA, van der Walt JH, Zoanetti DC. Immunization and anesthesia - an international survey. Paediatr Anaesth. 2006 May;16(5):514-22.DOI:10.1111/j.1460-9592.2006.01897.x PMID:16677260
22. Bertolizio G, Astuto M, Ingelmo P. The implications of immunization in the daily practice of pediatric anesthesia. Curr Opin Anaesthesiol. 2017 Jun;30(3):368-375. DOI:10.1097/ACO.0000000000000462. PMID:28490039
23. Alieff A. Der Einfluss von Operationene auf die Building des tetanusantitixintinters. Chirurg 1975;46:132-4.

24. Di Pietrantonj C, Rivetti A, Marchione P, Debalini MG, Demicheli V. Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Database Syst Rev. 2020 Apr 20;4(4): CD004407. DOI: 10.1002/14651858.CD004407.pub4. Update in: Cochrane Database Syst Rev. 2021 Nov 22;11:CD004407. PMID: 32309885;
25. APAGBI [homepage on the Internet]. London: Best practice guidance on immunization and surgery.Association of Paediatric Anesthetists of Great Britain and Ireland.2021:1-16. Avialable from: https://www.apagbi.org.uk/guidelines.
26. Popa A, Malos A, Cernea D. Recently immunization and anesthesia of the children.Curr Health Sci J 2009;35:201-204.DOI 10.12865/CHSJ.35.03.13
27. Shockley AN, Israel EN, Thomas CA. Risk of Inappropriately Timed Live Vaccination After Pediatric Cardiovascular Surgery. J Pediatr Pharmacol Ther. 2022;27(8):750-753. doi: 10.5863/1551-6776-27.8.750. Epub 2022 Nov 17. PMID: 36415771; PMCID: PMC9674358.
28. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health and Aged Care. Canberra [cited 2022]. Available from: http://www.immunisationhandbook.health.gov.au./.
29. Ministry of Health. Immunisation Handbook 2020. Wellington: Ministry of Health.Citation: Ministry of Health. Immunisation Handbook 2020. Wellington: Ministry of Health. ISBN 978-1-99-002923-3.
30. Shatz DV, Romero-Steiner S, Elie CM, Holder PF, Carlone GM. Antibody responses in postsplenectomy trauma patients receiving the 23-valent pneumococcal polysaccharide vaccine at 14 versus 28 days postoperatively. J Trauma. 2002 Dec;53(6):1037-42. DOI: 10.1097/00005373-199805000-00004. PMID: 9603075
31. Center for Disease Control.https//www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html. Updated Oct. 4, 2023.

