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Mini Review

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Role of Prehabilitation in Patients Undergoing Cancer Surgeries

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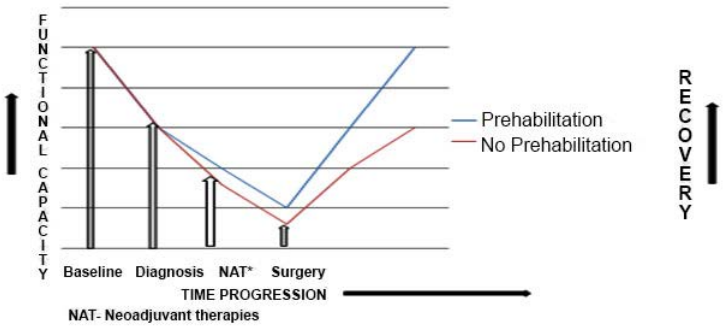
Cancer is the second leading cause of death worldwide and nearly 1 in 6 deaths is due to cancer. It accounts for 8.8 million deaths in 2015. The occurrence of cancer is increasing and new cases are expected to rise by about 70% over the next 2 decades.[1] With the advances in diagnostic and therapeutic procedures, more number of cancer patients will undergo curative surgical procedures. However, the mortality and morbidity rates after major oncological surgical resection are still high and range between 4%-10% and 20%-60%, respectively.[2,3] These high mortality and morbidity rates may be attributed to the patients' physical status, combined stressful impact of malignancy, neoadjuvant therapies (NAT), or the surgical procedure on patient during peri-operative period.

The post-operative period is not only associated with 20%-40% reduction in physiological and functional capacity, but also increased risk of post-operative complications which may have long-term effect on morbidity and mortality.[4]

In order to overcome current situation, the concept of 'prehabilitation' is increasingly being implemented. "Prehabilitation" in the pre-operative period provides an option to increase the physiologic reserve and functional capacity of the patient in order to hasten recovery and improve outcomes recovery and improve outcomes (Figure 1).[4]

Figure 1: Model of Prehabilitation Pre-operatively in Surgical Patients.



Cancer prehabilitation is "a process on the cancer continuum of care, that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes; physical and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments".[5] The optimal outcome for a cancer surgery requires panned protocol in the peri-operative period, starting from the pre-operative period and continued through the post-operative period, (Figure 2).[5]

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Figure 2: Interventions Delineated to Enhance Post-operative Outcome of Patients Undergoing Cancer Surgeries.

COMPONENTS OF SURGICAL PREHABILITATION PROGRAMME

Role of Structured Exercise Protocols in Surgical Prehabilitation of Cancer Patients

Among all the components, structured exercise protocols are of paramount importance. These protocols are heterogeneous in composition and include muscle strengthening and aerobic training activities like walking, cycling, jogging, and swimming. The frequency and duration of physical training exercises can be gradually increased. Regular exercise not only prepares cardiovascular, respiratory, musculoskeletal, and endocrine systems before the actual occurrence of physiological stress, but also helps in restoring insulin sensitivity that is lost with sedentary behavior.[6] While prescribing the exercise in specific "dose", duration and modality, feasibility of the exercises for the patient should be kept in mind while targeting the desired outcomes. Exercise intensities that are uncomfortable for the patient may lead to poor adherence and hence lower the success rate of programme. Recent evidence suggests that the type and amount of activity performed during non-exercise time should also be included in the exercise protocol to provide adequate recovery time.[7] The improvement of fitness during an exercise programme can be monitored by using modified Borg Scale, which assesses the level of perceived exertion in response to exercise.[8] In addition to this, sensor technology is being employed to objectively documents the increase in health related quality of life (QoL) with physical exercise (Table 1).[9]

Role of Nutritional Supplementation in Surgical Prehabilitation of Cancer Patients

Optimization of nutritional status is another vital component of prehabilitation programmes in cancer patients who are often frail with decreased muscle mass and low protein reserves. The etiology of malnutritionin cancer patients is multifactorial and encompasses direct tumor related mechanisms (e.g. obstruction), tumor induced metabolic derangements (insulin resistance, catabolism), gastrointestinal abnormalities (nausea, vomiting) due to disease itself and anti-cancer therapies.[10] Peri-operative treatment of disease related-malnutrition has been shown to reduce

Table 1: Components of the Prehabilitation Programme and Optimal Pre-operative Time Period.

Component	Prehabilitation intervention	Optimal time period preoperatively
Cachexia, myopenia, sarcopenia	Structured exercise protocol	2-6 weeks
Nutrition	Nutritional supplementation	6 weeks
Anxiety and depression reduction	Relaxation techniques Problem-solving Coping strategies	
Optimization of respiratory System	Smoking cessation Breathing exercises Incentive spirometry Pharmacotherapy Adequate hydration	6-8 weeks
Optimization of cardiovascular system	Optimization of medical therapy for underlying disease Lifestyle modification Smoking and alcohol cessation	8-12 weeks
Anemia correction	Depends on severity and time period available 1.Oral iron therapy 2.Parenteral iron therapy a)Intramuscular b)Intravenous	Expected rise in hemoglobin concentration: 1. 0.7 gm/100 ml/week 2.a) 0.7-1 gm/100 ml/week b)Transfused blood becomes functional only after 24-48 hours.

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the rate of morbidity and mortality.[11] Cancer patients also have increased protein demands required for the synthesis of hepatic acute phase proteins, proteins involved in immune function and wound healing.[12] The exercise regimen not only requires physical activity but also needs to be supplemented with protein supplements as to build up the muscles. Hence their nutritional status must be assessed by dietician for the risk of malnutrition and counseling regarding supplementation.

Dietary daily protein intake of 1.2 g/kg body weight must be targeted. Whey proteins may be considered as a good supplement for protein enhancement for skeletal muscle as it rich in leucine content and it also stimulates translation initiation of protein synthesis in skeletal muscle.[13] Whey proteins also exhibit anti-inflammatory effects by promoting synthesis of glutathione due to high cysteine content.[14] Furthermore, omega-3 fatty acids, particularly eicosapentaenoic acid and docosahexaenoic acid, which are found naturally in fish oils, should also be supplemented as they have been shown to reduce oxidative stress and inflammation in cancer and surgical patients.[15]

Role of Psychological Stress Reduction in Surgical Prehabilitation of Cancer Patients

The presence of psychological distress like anxiety and depression are commonly found in cancer patients. Pre-operative psychological distressis associated with higher levels of pain, non-compliance with medical treatment, diminished immune response, poor wound healing, longer hospital stayand increased risk of mortality.[16-18] The various interventions as a part of prehabilitation includes; deep breathing, progressive muscle relaxation and meditation, visualization yoga, music, guidedimagery and/or problem-solving, and coping strategies. These strategies not only help in overall improvement of patients in pre-operative status, but also enhance and reinforce patients' motivation to comply with other strategies of prehabilitation, like the exercise and nutritional aspects as well. As a result, techniques have been shown to improve the quality of life (QoL) by reducing anxiety, depression, severity of pain and fatigue.[19-21]

Role of Smoking and Alcohol Cessation in Surgical Prehabilitation of Cancer Patients

Smoking and alcohol consumption are commonly encountered lifestyle risk factors, that adversely affect the outcome after surgery. Alterations in pulmonary and cardiovascular functions, impaired wound healing, diminished immune response, increased risk of infections and bleeding episodes, delaying in administration of neoadjuvant therapy, increased recurrence, second primaries, and high mortality are all associated with smoking and alcohol consumption.[22-25]

These changes can be reversed to some extent by discontinuation in pre-operative period. Counseling with administration of continuous nicotine replacement therapy and Vareniciline either alone or in combination may be helpful in cessation.[26] Though the improvement in body after abstinence from smoking and alcohol starts from beginning itself, but recovery of specific organ dysfunctions varies with regards to time required for optimization of organ specific function (Table 2).[27]

MEASURING OF OUTCOMES AFTER SURGICAL PREHABILITATION

Outcome's measures that have been used to measure the effect of prehabilitation include; compliance to prehabilitation programme, 6MWT (the maximum distance the participant can walk in 6 min), anaerobic threshold (AT), Hospital Anxiety and Depression Scale (HADS), length of hospital stay, and postoperative complications using Clavien-Dindo classification, health-related QoL using 36-item short-list questionnaire (SL-36).[28,29]

CONCLUSION

To conclude, prehabilitation remains a important component of holistic management of an cancer patient. The outcome after surgical intervention would improve if timely interventions like nutrition, exercise etc as part of prehabilitation becomes a integral

Table 2: Beneficial Systemic Bodily Effects of Alcohol and Smoking Abstinence.

Alcohol abstinence	Recovery	Smoking abstinence	Recovery
Immune competence	2-8 weeks	Immune competence	2-6 weeks
Wound healing	8 weeks	Wound healing	3-4 weeks
Endocrine stress response	2-12 weeks	Pulmonary function	6-8 weeks
Pulmonary function	6-8 weeks		
Bone regeneration	<6 months		
Haemostasis	1-4 weeks		
Cardiac function • Without symptoms • With severe failure	 • 1 month • 1-6 months		

part of overall management.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Case Report

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A Rare Septic Transfusion Reaction: Case Report

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BACKGROUND

Transfusion of packed red blood cells (PRBCs) is indicated in severely bleeding patients and in anemic patients who require increased oxygen-carrying capacity. According to the 2016 AABB guidelines, for patients who are hemodynamically stable without active bleeding, PRBC transfusion is likely indicated for hemoglobin of 6 to 7 g/dL.[1] A higher threshold (<8 g/dL) is indicated in patients with cardiovascular disorders.

Transfusion of PRBCs is associated with an increased risk of adverse reactions. Complications may occur over a wide range of time from immediately during transfusion to days afterwards. These include allergic reactions, febrile non-hemolytic reactions, hemolysis, transfusion associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), transfusion-transmitted pathogens, and immune-mediated reactions. Transfusion-associated sepsis (TAS) is an acute nonimmune reaction that is more common with platelet transfusion at an incidence of 1:25,000 for pooled platelets and 1:50,000 for single donor platelets. The estimated incidence of TAS in PRBC transfusion is 1:250,000.[2] Due to low storage temperatures of PRBCs, the most significant hazards are psychrophilic or cryophilic organisms that grow in cold (4 °C) temperatures and use citrate as a nutrient such as *Pseudomonas* species, *Yersinia enterocolitica*, *Campylobacter*, and *Serratia* species.[3] Contamination of PRBC units most likely occurs due to non-aseptic technique during phlebotomy, contaminated equipment used for blood collection and processing, and rarely due to its presence in the donor blood at the time of donation.

CASE

A 29-year-old woman with microangiopathic hemolytic anemia associated with Systemic Lupus Erythematosus (SLE) and Lupus nephritis was admitted to the hospital for lupus flare. Her medical history indicated that she received Rituximab and Cytoxan infusion during her previous admission and had been receiving Cytoxan infusions as an outpatient. Her current hospital course was complicated by thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), renal failure, and pericardial effusion with tamponade. Plasmapheresis procedures were initiated twice a week concurrent with hemodialysis three times a week as an outpatient.

A few weeks later, the patient came to the apheresis unit for her regular out-patient plasma exchange procedure. She felt well and did not report any pain, fever, chills, or shortness of breath. Her pre-procedure vitals were stable (blood pressure (BP) 138/75 mmHg, hematocrit (HCT) 23, platelet count (PLT) 110). Her only complaint was fatigue which was thought to be secondary to hypokalemia (K+ was 2.8 mEq/L two days earlier and was currently 3.3; normal range 3.2-5.5 mEq/L). She also complained of loose stools after taking labetalol, which was a common side effect for her. However, this may have been due to *Costridium difficile* as she tested positively on admission to the ICU. She took all of her medications earlier that morning except labetalol (800 mg twice/day with instructions to hold for systolic blood pressure (SBP)<113 mmHg) because her SBP at home was 106 mmHg. The apheresis procedure started

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at 8:40 am for 1x volume plasma exchange. The patient was pre-medicated with Tylenol (650 mg PO) and hydrocortisone (100 mg IV) and tolerated apheresis well. The patient received 11 units of plasma during the apheresis procedure, which was concluded successfully at 10:30 am. Due to a chief complaint of fatigue and a HCT of 23, one unit of PRBCs was ordered by her hematologist to be transfused after the apheresis procedure.

Her current type and screen test (TST) result was O-Negative (consistent with her medical record) with a positive antibody screen identified as Anti-D due to Rho Immune Globulin. A full-crossmatched, O Negative PRBC was released for transfusion at 10:42 am. The PRBC transfusion was started at 10:52 am at a rate of 100 mL/hr. The patient's pre-transfusion vitals were: temperature=37 °C, BP 138/75, and pulse 97. At 12 pm the patient experienced a sudden sharp occipital headache that she rated as 7 (on a scale of 1-10), back pain, heaviness of her lower extremities, and reported "*I cannot get comfortable*". The transfusion was stopped. BP was found to be slightly elevated at 154/94 mmHg. She received labetalol (800 mg PO), Lasix (20 mg IV), oxycodone (5 mg PO), Tylenol (650 mg PO), and hydrocortisone (100 mg IV). Twenty minutes later the patient felt better and her BP was 159/96 mmHg; another dose of Lasix (20 mg IV) was administered. Following a consultation with one of the hematology fellows, the apheresis nurse was advised that this was most likely an allergic reaction and the nurse was informed that she could restart the PRBC transfusion. As the patient was feeling better, the same PRBC transfusion was restarted 1.5 hours later at a rate of 100 mL/hr. BP then was 104/54 mmHg, heart rate 117 bpm, and temperature 37.6 °C. Within 15 minutes of restarting the transfusion, the patient became pale and her BP dropped further to 98/47 mmHg with a heart rate of 115 bpm. The patient expressed concern about her blood pressure so to overcome this slight hypotension the transfusion rate was increased to 150 mL/hr. Five minutes later she was reported to have rigors, was crying and reported being very scared and emotional, and complaining of crushing chest pain and shortness of breath. At this time, BP was found to be 87/40 mmHg, heart rate in the 50s, respiration in the 40s, temperature of 37.3 °C, and O_2 saturation low at 60% on room air and 80% on 100% oxygen non-rebreather mask. The PRBC transfusion was discontinued after a total of 150 mL was administered, and the patient received Benadryl (50 mg IV), hydrocortisone (100 mg IV), and Demerol (25 mg IV) and was sent to the emergency department (ED) for the crushing chest pain. Upon arrival in the ED the patient felt warm to the touch and had a temperature of 38.6 °C. One of the patient care teams evaluating the patient felt the reaction was acute and was likely transfusion-related acute lung injury (TRALI). The remaining PRBCs and tubing were sent to the blood bank to complete a transfusion reaction workup. A fresh patient's blood sample was also sent to the microbiology laboratory for a sterility blood culture.

A Transfusion Reaction workup was initiated immediately at the blood bank. Clerical errors were ruled out. No hemolysis in the returned PRBC unit was obvious (19-days-old). However, moderate hemolysis in the patient's post-reaction specimen was observed. The post-reaction patient testing was confirmed to be O Negative with a negative direct antiglobulin test (DAT). Repeat ABO testing of the PRBC unit matched the collection center label. Repeat testing of the patient's pre-reaction specimen agreed with the original results. Repeat testing of the full-crossmatch to both the patient's pre-reaction specimen and post-reaction specimen confirmed compatibility of the unit.

It was noted by one of the blood bank staff that the PRBC looked darker in color (Figure 1A, 1B and 1C). This color became progressively darker the longer the unit was exposed to room temperature. Several of the segments attached to the bag were also darker and several (those farthest from the bag) remained bright red with a normal appearance. Due to the moderate hemolysis in the patient's post-reaction specimen, the

Figure 1: A) Represents a Dark Red Color of Contaminated PRBC (Actual Photo of Contaminated PRBC); B) Represents the Bright Red Color of Normal ~20 Days Stored PRBC; C) Segments Attached to the Contaminated Unit, some being Dark and some being Normal in Color.

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blood bank interpreted the transfusion reaction as a possible acute hemolytic reaction with no further transfusions allowed at the time. The product bag and all segments were sent to the Microbiology laboratory for gram stain and sterility blood cultures. Meanwhile, the patient's temperature was reported to be up to 38.6 °C. Two hours later the gram stain of the PRBC bag was reported positive for gram variable bacilli. Three days later the sterility blood culture indicated *Serratia liquefaciens* with colony forming units/mL too numerous to count (Figure 2A and 2B). The noticeably darker segments attached to the unit were also found to contain *Serratia liquefaciens* while the segments that remained normal in appearance had no growth. The same bacteria were retrieved in the patient's post-transfusion blood sample. The interpretation of the transfusion reaction was modified to bacterial sepsis caused by contamination of the PRBC unit.

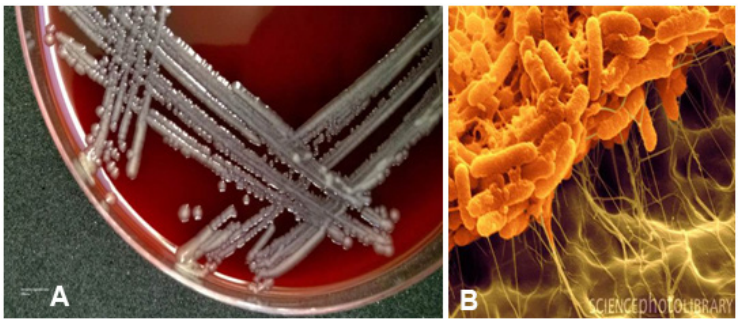
While in the ED, the patient received Solumedrol (125 mg IV) and Lasix (20 mg IV). Her chest X-ray showed moderate pulmonary edema along with worsening pleural effusion. She was then admitted to the medical ICU for septic shock management, which included broad spectrum antibiotic therapy and inotropic support with norepinephrine bitartate (Levophed, Phizer, New York, New York, USA) infusion. Infectious disease was consulted and she was treated with ceftriaxone (2 g IV/day for 17 days) and tobramycin (300 mg IV/day for 6 days). She was also treated for *Clostridium difficile*, which she likely was infected with prior to admission, and completed a course of metronidazole (500 mg IV/8 hours for 23 days) and vancomycin (1,000 mg IV for 2 days and 125 mg PO/6 hours for 3 doses). Antibiotic treatment was effective as evidenced by improvement in leukocytosis per the infectious disease service.

At the time of admission to the ICU the patient displayed signs of cardiac tamponade due to a worsening chronic effusion. A drain was placed and 800 mL of fluid was removed with another 250 mL drained in 24 hours. After the procedure the norepinephrine bitartrate infusion was weaned and the patient was transitioned to a vasopressin (Vasopin, Samarth Pharma Pvt. Ltd., Mumbai, Maharahtra, India) infusion for 24 hours. Continuous veno-venous hemodialysis (CVVHD) was initiated due to her chronic renal failure with orders to remove 250 mL of fluid per day above baseline. On day 3 of hospitalization she developed decompensated hypoxic respiratory failure and pulseless electrical activity arrest several days later and received 50 minutes of CPR and 20 minutes of chest compressions and shocks. CVVHD was stopped and the patient received 3L of normal saline for volume support. At the time of intubation the patient had copious amounts of pink frothy secretions. Epoprostenol (FLOLAN GlaxoSmithKline, Brantford, UK) was started and the patient required 100% FiO_2 and 20 mmHg of positive end expiratory pressure to treat pulmonary hypertension. She was subsequently placed on Artic Sun Protocol; a temperature management system by Medivance (Louisville, CO, USA). This system uses water-circulating gel pads placed on the patient's skin covering approximately 40% of the patient's body surface area. This treatment is considered moderate hypothermia and reduces the core body temperature to between 32 °C to 35 °C. After cardiac arrest oxygen stores are depleted and the brain turns to anaerobic metabolism within minutes. This causes cellular trauma which leads to electrolyte imbalance, cytotoxic edema and cell death. Even after oxygen is restored to the brain, inflammation processes continue to injure the brain. This is known as reperfusion injury and may last for up to 48 hours. Induction of hypothermia decreases the cerebral metabolic rate 6 to 7% for every 1 °C drop in body temperature, thereby reducing the inflammatory response and preventing neurological injury.[5,6] Additionally, continuous chemical paralytic and sedation infusions were started for five days. Full neurologic recovery was accomplished after 14 days in the ICU. Initial confusion and restlessness was attributed to possible encephalopathy but was more likely related to narcotic withdrawl and ICU psychosis.

DISCUSSION

The genus *Serratia* consists of at least 15 species that are facultative anaerobic gram-negative rods of the *Enterobacteriaceae* group. *Serratia marcescens* is an established human pathogen associated with urinary tract infection, pneumonia, and blood stream infections. *Serratia* species may be most known for their proportion of eye infections, second only to *Pseudomonas aeruginosa*. Other common species include *S. liquefaciens*, *S. plymuthica*, and *S. rubidaea*. Human infections caused by *Serratia* species are thought to arise from exogenous environmen-

Figure 2: A) Serratia liquefaciens on Blood Agar. August 2014. www.microregistrar.com. May 2017 B) Serratia liquafaciens Biofilm SEM. Scimat/Science Photo Library. May 2012. microbewiki.kenyon.edu. May 2017.



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tal sources rather than from commensal flora. The incidence of *Serratia* infections is estimated to be 10.8 per 100,000 people annually, with a hospital onset rate of 0.4 per 1000 inpatient discharges according to a single Canadian study.[6]

To reduce the likelihood of contamination in blood collection, the WHO recommendation for blood drawing is that the skin around the collection site be carefully examined and cleaned before the needle is inserted.[7] Skin disinfection reduces the skin bacterial load, but a sterile venipuncture cannot be guaranteed due to inaccessibility of organisms present in sebaceous glands and hair follicles.[8]

In this case, our blood collection center was notified of the recipient complication and they investigated the donor and the collection process. In their investigation they found that the donor was in good health and the phlebotomy site was acceptable. Although, the exact source of contamination could not be determined, the phlebotomy staff involved was observed to ensure appropriate arm scrub and preparation techniques were followed. It is most probable that the bacterial contamination originated from an environmental source and was introduced into the blood unit during collection or processing. However, the fact that some of the farthest segments tested negative for the bacteria indicates that the contamination most likely occurred from environmental factors during unit processing.

While the exact cause may not be determined, there is a notable learning opportunity in how this case progressed. Roughly an hour after the transfusion was started, it was stopped. It is occasionally stated that allergic transfusion reactions to plasma are an exception to the rule and can be restarted. Transfusions should never be restarted after discontinuation, regardless of the type of reaction. Also, the Transfusion Medicine Service was never consulted during this reaction. It should not be assumed that a reaction is allergic in nature unless discussed with a blood bank supervisor or transfusion medicine faculty member. Restarting this PRBC after being at room temperature for several hours, and subsequently increasing the infusion rate, allowed an additional dose of bacterial contamination to enter the patient's blood stream and further complicated her clinical picture. A suspected transfusion reaction should always be immediately stopped and reported to the Transfusion Medicine Department. They are most qualified to advise the care team on the best plan of action moving forward. Transfusion reaction signs and symptoms do not always follow the "expected guidelines." The patient's vital signs and symptoms in this case could have easily been interpreted as a possible hemolytic, TRALI, or TACO reaction, all of which were mentioned in the patient's medical record at some point. Symptoms of agitation, feeling uncomfortable, anxious, or emotional (the sense of "impending doom") should always be taken very seriously and a transfusion should be stopped immediately. These symptoms reported by the patient, are often more critical than vital signs and often implicate a serious reaction.

CONCLUSION

In conclusion, any indication of a possible transfusion reaction warrants investigation by the transfusion medicine service. When there is a suspicion of any reaction, even a mild case, the transfusion must not be restarted but should be sent for additional evaluation and testing in order to prevent a catastrophic event such as this. When blood product contamination is identified, all other products from the donor are quarantined in order to avoid additional complications to other recipients. This case highlights the important role that transfusion medicine practitioners play in maintaining a safe blood supply and ensuring the best outcomes for transfused patients.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

Verbal consent was taken from the patient.

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Review

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Role of Dexamethasone in Peri-operative Anesthesia Management: A Review of Literature

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ABSTRACT

Dexamethasone has been used widely in clinical specialties including anesthesia. It is regarded as one of the ideal peri-operative agent being readily available, cheap, anti-inflammatory agent, prevents and treats post-operative nausea and vomiting (PONV), promotes appetite, suppress inflammation, a good analgesic agent both as intravenously or as an adjuvant to peripheral nerve blocks, it provides a sense of well-being and is considered to have a good quality of recovery and early discharge in patients from anesthesia. Controversial role of dexamethasone in causing post-operative surgical site infections have been solved and overall adverse effects of dexamethasone are rare and its benefits out-weighs the risks involved. The author did a literature search in Google Scholar and PubMed databases (latest articles related to the role of dexamethasone in peri-operative period over a period of two years 2015-17).

KEY WORDS: Dexamethasone; Peri-operative agent; Anesthesia.

KEY MESSAGES: Dexamethasone has a tremendous role in preventing post-operative nausea and vomiting, it has a fair analgesic action if given intravenously, epidurally or perineurally, patients receiving dexamethasone have enhanced recovery profiles after surgery and single dose would usually not increase the risk of surgical site infections. Overall adverse effects of dexamethasone are rare and its benefits out-weighs the risks involved.

ABBREVIATIONS: COPD: Chronic Obstructive Pulmonary Disease; PONV: Post-operative Nausea and Vomiting; TIVA: Titrated Total Intravenous Anesthesia; AVN: Avascular Necrosis; POCD: Post-operative Cognitive Decline; TPVB: Thoracic Paravertebral Block; PACU: Post Anesthesia Care Unit; GABA: γ-aminobutyric acid; DNB: Dental Nerve Block; TMS: Third Molar Surgery.

INTRODUCTION

Glucocorticoids have been used to reduce inflammation and tissue damage in a variety of conditions, including inflammatory bowel disease, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD), acute laryngotracheobronchitis, cerebral edema, severe allergy or anaphylaxis, promote lung maturation in pre-term and some malignancies to counteract inflammatory and nausea vomiting side effects of chemotherapeutic agents. Dexamethasone is a synthetic glucocorticoid which has minimal mineralocorticoid activity. It is a potent anti-inflammatory drug with thirty to forty times the potency of hydrocortisone and is up to sixteen times as potent as prednisolone.

AN IDEAL PERI-OPERATIVE AGENT AND MECHANISM OF ACTION

Dexamethasone has been used widely in clinical specialties including anesthesia. The biological half-life is about 3 hours, although the duration of action may be much longer. Dexamethasone is bound to plasma proteins in much lower-levels than other glucocorticoids. Hepatic metabolism (both glucuronidation and sulfation) occurs to produce inactive metabolites, with

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65% of the dose of dexamethasone excreted in the urine within 24 hours, with less than 3% unchanged.

It is regarded as one of the ideal peri-operative agent being readily available, cheap, anti-inflammatory agent, prevents and treats post-operative nausea and vomiting (PONV), promotes appetite, suppress inflammation, a good analgesic agent both as intravenously or as an adjuvant to peripheral nerve blocks, it provides a sense of well-being and is considered to have a good quality of recovery and early discharge in patients from anesthesia. It has a complex mechanism of action involving binding of steroid ring to the receptor effect site, which results in gene transcription, and resulting in decreased release of mediators like bradykinin, IL 1, 2 and 6, resulting in pain relief.

DEXAMETHASONE: ROLE IN PONV

The mechanism of action of dexamethasone as an antiemetic agent, is unknown, there are various postulated mechanism is depletion of γ-aminobutyric acid (GABA) stores, and reduction of blood brain barrier to emetogenic toxins, inhibition of central prostaglandins and serotonin. There are tremendous literature available which suggest that dexamethasone reduce the incidence of post-operative nausea and vomiting. In one of the biggest DREAMS trial collaborators, 1350 participants were randomly allocated to dexamethasone and control group, and it was found that a single dose of 8 mg dexamethasone reduced the incidence of nausea and vomiting till 24 hours and rescue anti-emetics were not required till 72 hours in patients who underwent bowel surgeries with no adverse events.[1]

Vlok found that there is a significant reduction in post-operative nausea and vomiting and post-operative pain as compared to tramadol, pethidine, magnesium sulphate and tramadol.[2] Sehavat et al suggested that a single prophylactic dose of dexamethasone 8 mg after an operation can reduce post-operative nausea and vomiting.[3] Naryanappa et al suggested that combination of dexamaethasone and ramosetron is more effective than palonosetron in PONV prevention, and they did their study in gynecological surgeries under spinal anesthesia.[4]

While there were researchers who were publishing astonishing results of dexamethasone as a good prophylactic and therapeutic agent for PONV, there were concerns which were raised suggesting the risk of surgical site infections. Kurz et al did investigations and found that a single dose of dexamethasone used in peri-operative period does not increase the risk of surgical site infections.[5] However, the combination of dexamethasone and ondansetron was not effective in preventing PONV or severe PONV in obese patients undergoing laparoscopic sleeve gastrectomy after titrated total intravenous anesthesia (TIVA).[6]

DEXAMETHASONE: ANTI-INFLAMMATORY ACTION

Research on clinically significant anti-inflammatory action of dexamethasone has been studied in dental, ear nose and throat (ENT) surgeries. Dexamethasone in dosage of 0.5 mg/kg reduces edema and also has been found to modulate bronchial hyper reactivity in asthmatic patients. Yang et al have found that a single bolus of 10 mg dexamethasone at the time of induction in thyroidectomies reduced the incidence as well as severity of post-operative sore throat during swallowing at 24 hours after surgery.[7] However, Kamranmanesh et al studied the role of dexamethasone in pediatric age group and found that the incidence of cough (31% *vs*. 34%), laryngospasm (16% *vs*. 14%), apnea (9% *vs*. 5%), desaturation (4% *vs*. 5%), bronchospasm (14% *vs*. 7%), vomiting (4% *vs*. 6%), and post-operative symptoms (8% *vs*. 7%), were less but not significantly different in patients receiving dexamethasone and placebo group.[8] Lim et al in their prospective randomized double-blind study suggested that a single pre-operative dose of dexamethasone *versus* methylprednisolone was equally effective in reducing post-operative swelling and trismus.[9]

EFFECT ON NEUROMUSCULAR BLOCKADE

So et al have found that a single dose of dexamethasone in dosage of 8 mg administered 2-3 hours prior to surgery have shortened the onset and recovery times of cis-atracurium induced block by 15% by enrolling one hundred seventy patients into 3 groups, and patients received 8 mg dexamethasone. Three minutes after anesthesia induction, intubation was performed without neuromuscular blockers, and acceleromyography was initiated. All patients received 0.05 mg/kg cisatracurium; the onset time and recovery profiles were recorded. The recovery time [mean (95% CI) minutes] was significantly hastened in dexamethasone group [28.5 (27.3-29.6)] compared to that in control group [32.3 (31.0-33.6)] (p<0.001) and control group [30.9 (29.9-31.8)] (p=0.015). The total recovery time was significantly hastened more in dexamethasone group [47.1 (45.5-48.6)] than group control [52.8 (51.6-54.0) minutes] (p<0.001) and control group [50.5 (48.7-52.3) minutes] (p=0.008).[10]

ANALGESIC EFFECT OF INTRAVENOUS DEXAMETHASONE

Analgesic action of dexamethasone has been found in dental surgeries (e.g., tooth extraction), ENT surgeries (e.g., mastoidectomy, tonsillectomy, adenoidectomy, etc.), ano-rectal surgeries. Even its role has been well defined in total knee arthroplasty, Samona et al have used a single dose of dexamethasone and have found that there is significant reduction in narcotic consumption and significant decrease in pain scores at 24 hrs. It also appears to be a safe modality in patients undergoing total knee arthoplasty (TKA) with no increase in wound related complications.[11] Jain et al have compared different dosage of dexamethasone and have found that 16 mg reduces post-operative pain on motion at 24 and 36 hours.[12] Role of intravenous dexamethasone has not just confined to systemic analgesia rather its role has been defined in prolonging the peripheral nerve blockade. Addition of dexa both intravenously and caudally as an adjuvant to caudal ropivacaine has been found to reduce the intensity of post-operative pain and prolonging the post-operative analge-

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sia.[13] Chalifoux have found that low doses of intravenous dexamethasone (4 mg and 10 mg) significantly prolongs the analgesic duration of interscalene block.[14]

The mean visual analog scale (VAS) was significantly lower in the Group C for up to 24 h following the caudal block. No significant hemodynamic changes were noted in any of the groups. The intravenous dexamethasone group showed higher blood glucose levels at 24 h but was not clinically relevant. These results suggest that injection dexamethasone is a safe adjunct to caudal ropivacaine in lumbosacral spine surgeries.[15] The authors concluded that administration of dexamethasone 8 mg intravenously prolongs the duration of post-operative analgesia and sensory block in patients undergoing lower segment cesarean section under spinal anesthesia.[16]

ROLE OF EPIDURAL DEXAMETHASONE IN CENTRAL NEURAXIAL BLOCKADE

The mechanism of action by which epidural or perineural dexamethasone acts is unknown, some believe it to be because of direct membrane stabilizing effect on nerves or direct action on spinal cord by means of transcription factors like nuclear factor kappa B (NF- κB). Hong et al have used epidural dexamethasone and found that 10 mg epidural dexamethasone was more effective than lower dosage in patients undergoing gastrostomy, associated with moderate to severe intensity of pain. Total fentanyl consumption was also significantly less in dexamethasone group and no difference in adverse events like hypotension, bradycardia, post-operative nausea and vomiting and urinary retention were found.[17]

PERINEURAL DEXAMETHASONE

Dexamethasone prolongs the action of lignocaine 2% in dental nerve block (DNB) for third molar surgery (TMS). Study found maximum duration of DNB in study group (SG) was 248.88 min and in control group (CG) was 175.44 min.[18] In a study by Zhao et al it was found that perineural dexamethasone prolongs the analgesic duration as compared to intravenous route only when epinephrine is coadministered. Without epinephrine, the two modalities show equivalent effect as adjuvants on regional anesthesia.[19] Razavizadeh et al affirmed that adding dexa to bupivacaine in patients undergoing herniorrhaphy in inguinal area significantly prolongs the duration of post-operative analgesia.[20] Ribeiro et al have found a significant increase in duration of analgesia in dexamethasone group in 0.1 mg/kg dosage as compared to placebo with bupivacaine in upper limb surgeries in pediatric age group, The duration of analgesia in the group BD was 27.1±13.4 hours and was significantly higher as compared to the group B, in which it was 13.9±11.3 hours (p<0.05) receiving dexamethasone (0.1 mg/kg) as an adjunct to bupivacaine 0.125%.[21]

Similar result has been shown by Akram et al in finding improved tolerance in hand and forearm surgeries and better analgesia in group receiving dexamethasone as compared to lignocaine and ketorolac, and the difference being statistically significant.[22]

Addition of dexamethasone to ropivacaine in transversus abdominis plane (TAP) blockade has also been found to have prolonged analgesia and reduced analgesic requirement in total abdominal hysterectomy. Post-operative VAS pain scores were significantly lower at 4, 6, and 12 h in Group Ropivacaine Dexamethasone (RD) as compared to Group Ropivacaine (R) alone (p<0.05). Significantly longer analgesia (13.2±7.6 *vs*. 7.1±4.6 h, p<0.001) with lesser tramadol requirement in first 24 h (50.2±34 *vs*. 94±35 mg, p<0.001) were observed in Group RD as compared to Group R.[23]

Dexamethasone 300 µg/kg with ropivacaine intraarticular has a superior analgesic efficacy a much prolonged post-operative pain relief, minimal post-operative analgesia requirement and better patient compliance with negligible side effects. Liu et al did a prospective observational study and used a single shot of bilateral thoracic paravertebral block (TPVB) with 25 ml of 0.2% ropivacaine and 5 mg dexamethasone in combination for both sides at the 8th thoracic transverse level (T8) performed on 201 participants who complained moderate to severe pain on arrival to postanesthesia care unit (PACU) after laparotomy. The VAS pain scores at rest and on cough were 7.9±1.6 and 8.7±1.3 respectively pre-bilateral TPVB. The VAS pain scores at rest and on cough were significantly decreased to 1.1±1.2 and 2.1±1.6 respectively (p<0.001) at 60 min after bilateral TPVB and to 2.1±1.7 and 3.8±1.9 at rest and on cough respectively ((p<0.001) at 24 h after bilateral TPVB. At 10 min post-bilateral TPVB, only systolic blood pressure was reduced from 122±19 mmHg to 111±18 mmHg (p=0.007) but then gradually became stable.[24] In addition to its useful effects, dexamaethasone has been tried in combination to ropivacaine in ankle block and the combination has been found to improve pre-emptive ankle block by decreasing post-operative pain intensity and analgesic consumption with minimal post-operative complication.[25] However, low dose dexamethasone 2 mg has been found to have only modest and inconsistent effect of questionable clinical relevance on block duration.[26]

A concern has been raised in a meta-analysis carried out by Chong et al and it was suggested that perineural dexamethasone prolongs the duration of analgesia and the magnitude of effect of 3.77 hours (95% confidence interval [CI], 1.87-5.68 hours; p<0.001) compared to IV dexamethasone, with high statistical heterogeneity) raises the question as to whether perineural dexamethasone should be administered routinely over its IV counterpart or reserved for selected patients where such prolongation would be clinically important. For secondary outcomes, perineural dexamethasone prolonged the duration of both motor (3.47 hours [95% CI, 1.49-5.45]; p<0.001) and sensory (2.28 hours [95% CI, 0.38-4.17]; p=0.019) block compared to IV administration. Furthermore, perineural dexamethasone patients consumed slightly less oral opioids

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at 24 hours than IV dexamethasone patients.[27]

ROLE OF DEXAMETHASONE IN SHIVERING

Moeen et al have shown in their study done during transurethral prostatectomy that intrathecal dexamethasone was as effective as intrathecal meperidine in attenuation of shivering compared to placebo under spinal anesthesia with less adverse events. The number of patients with shivering was higher in Group Control (C) (13) than in Group Dexamethasone (D) (2) and Group Meperidine (M) (3) with no differences between Group D and M; p=0.001. Intensity and recurrence of shivering and dose of IV meperidine used to treat shivering were higher in Group C compared to Group D and Group M; p=0.01, p =0.064, and p=0.004, respectively.[28]

MISCELLANEOUS ROLE OF DEXAMETHASONE

Karman et al suggested that the co-administration of dexamethasone and sevoflurane may ameliorate short-term and long-term cognitive dysfunctions induced by sevoflurane in adult rats. Sevoflurane may impair spatial learning and short-term and long-term memories in adult rats.[29]

In severe to profound sudden deafness refractory to conventional ST, the daily perfusion of 4 mg/ml DEX through an intratympanic catheter is an easy, well accepted procedure that enables patients to receive a drug in the middle ear in a repeatable or sustained form, with minimal discomfort and a partial rescue (67.86%) and a speech recognition gain of 39% as suggested by Zanetti et al.[30]

CONTROVERSIAL ROLE IN WOUND INFECTION

In the largest ENIGMA II TRIAL, there were registered 5499 subjects, and it was found that dexamethasone administration was associated with a decrease in fever on days 1-3 [182 (8.4%) *vs*. 488 (14.7%); RR 0.61; 95% CI 0.5-0.74; p<0.001] and shorter lengths of stay in hospital [propensity score-adjusted median (IQR) 5.0 (2.9, 8.2) *vs*. 5.3 (3.1, 9.1), p<0.001]. Neither diabetes mellitus nor surgical wound contamination status altered these outcomes. Dexamethasone was administered to 2178 (40%) of the 5499 subjects included in this analysis and was not associated with wound infection [189 (8.7%) *vs*. 275 (8.3%); propensity score-adjusted relative risk (RR) 1.10; 95% confidence interval (CI) 0.89-1.34; p=0.38], severe post-operative nausea and vomiting on day 1 [242 (7.3%) *vs*. 189 (8.7%); propensity score-adjusted RR 1.06; 95% CI 0.86-1.30; p=0.59], quality of recovery score [median 14, interquartile range (IQR) 12-15, *vs*. median 14, IQR 12-16, p=0.10), length of stay in the post-anesthesia care unit [propensity score-adjusted median (IQR) 2.0 (1.3, 2.9) *vs*. 1.9 (1.3, 3.1), p=0.60], or the primary outcome of the main trial.[31] And it was concluded that dexamethasone administration to high-risk non-cardiac surgical patients did not increase the risk of post-operative wound infection or other adverse events up to day 30, and appears to be safe in patients either with or without diabetes mellitus. Also in retrospective analysis done by Richardson et al, a single intravenous peri-operative dose of dexamethasone had no statistically significant difference in the rate of post-operative joint infections after total hip or knee arthroplasty.[32]

QUALITY OF RECOVERY

Mihara et al have determined the quality of recovery using QoR-40 questionnaire and indicated that peri-operative dexamethasone administration may improve short-term (i.e., one day) quality of recovery after general anesthesia and surgery.[33] In another randomized control trial done by Sakamoto et al, have demonstrated a better quality of recovery in patients' receiving dexamethasone compared to control for a bilateral inguinal hernia repair surgery.[34] Use of dexamethasone prior to vaginal reconstructive surgery was associated with less nausea/vomiting and need for antiemetics as well as greater success with voiding trials. Furthermore, quality of recovery was enhanced, suggesting use of dexamethasone should be considered for these patients as suggested by Pauls et al[35] Valentin et al, have revealed that dexamethasone can reduce the incidence of post-operative cognitive decline (POCD) in elderly patients undergoing surgery, especially when associated with BIS 46-55. The effect of dexamethasone on S100β might be related with some degree of neuroprotection. Neuropsychological tests showed that dexamethasone associated to BIS 46-55 decreased the incidence of POCD, especially memory and executive function. The administration of dexamethasone might have prevented the post-operative increase in S100β serum levels.[36]

ADVERSE EFFECTS OF DEXAMETHASONE

There are few authors who suggest that peri-operative administration of dexamethasone during neurosurgical procedures can cause significant increase in blood glucose concentration especially in patients who receive dexamethasone intra-operatively.[37]

Dexamethasone is particularly contraindicated in systemic fungal infections and before the administration of live or attenuated vaccines because the response to these vaccines cannot be predicted. The use of dexamethasone in oral cancer patients with microvascular reconstruction did not provide a benefit. More major complications, especially infections, occurred in patients receiving dexamethasone. Their data thus did not support the use of peri- and post-operative dexamethasone in oropharyngeal cancer patients undergoing microvascular reconstruction.[38]

Dexamethasone 8-10 mg is associated with a significantly greater peri-operative increase in blood glucose compared with a 4 mg dose. This model estimated the increase in post-operative glucose to be 25 mg/dL higher over 24 hours with dexamethasone 8-10 mg than with 4 mg (95% confidence limits, 18-32 mg/dL).[39]

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Avascular necrosis (AVN) of both the humeral and femoral heads is a known complication of chronic steroid use; however, single dose of dexamethasone usually won't cause AVN. Dexamethsone induced pruritus is a known entity, and usually patients experience genital or anorectal or perineal pruritus. It is usually short lived lasting 2-45 seconds and phosphate group is the postulating factor for the same. It is more commonly seen in females and is avoided by either giving dexamethasone slow or by addition of lidocaine.[40]

LIMITATION OF THE STUDY

This is not a systematic review and remains author's interpretation.

CONCLUSION

Considering the benefits of dexamethasone, there is increasing trend towards its use. Not just it is helpful in preventing post-operative nausea and vomiting, also it has a good analgesic action both intravenously, epidurally or perineurally. Patients have enhanced recovery profiles after surgery and single dose would usually not increase the risk of surgical site infections. It has an enhanced anti-inflammatory action and is a preferred drug during inflammatory situations like asthma, chronic obstructive pulmonary disease (COPD), laryngotracheal bronchitis and laryngospasm. Controversial role of dexamethasone in causing post-operative surgical site infections have been solved and overall adverse effects of dexamethasone are rare and its benefits out-weighs the risks involved.

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Opinion

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Mind the Gap Between the Bench and the Bed: The General Anesthetics-Induced Neurotoxicity in the Real World

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From the very beginning of Morton's successful demonstration of surgical anesthesia, reversibility has been identified as one of the unique characteristics of anesthesia. However, recent studies just reveal the opposite; general anesthetics (GAs) produce long-term, if not permanent, effects in the human brain, especially in the immature brain, at clinically relevant concentrations for clinical relevant durations, so-called the neurotoxicity of GAs on immature brains.[1] The neurotoxicity has been demonstrated with all types of GAs, including volatile anesthetics, benzodiazepine, propofol, and N-methyl-d-aspartate (NMDA) antagonists.[2] Although, the underlying mechanisms have not been well-illustrated, it has been generally accepted that the neuroinflammation plays a vital role in the pathogenesis of GAs-induced neurotoxicity. Due to huge impact of this subject (animal studies showed that both fetal and early post-natal exposure to GAs caused neurotoxicity), FDA issued a change in labeling regarding the safe use of anesthetic and sedative agents[3] and suggest delaying pediatric surgerie if possible, to avoid repeated or lengthy exposure to GAs in children under the age of 3 or in pregnant women during their third trimester.

However, most of the adverse results came from animal or *in vitro* studies, while most of the human trial reveal negative results, which indicate that single exposure to GAs at early days in their life caused no neurotoxicity in children.[4-6] Even with multiple exposures, the differences are generally very small.[7]

Clearly, there is a huge difference between the animal and human studies designs. In animal studies, subjects were exposed to GAs alone, without any surgical manipulation, in order to observe the isolated effect of GAs on neurodevelopment. However, in the real world, it is unlikely for our young patients to receive GAs alone, without any surgical procedures. On the other hand, most of the surgical procedures cannot be performed without anesthesia. Therefore, young children receiving minor surgery (such as inguinal hernias, circumcisions, cystoscopies, and pyloromyotomies) were included for these clinical trials,[8] for which it is possible to perform without anesthesia or with light sedation only.

The majority of pediatric surgeries cannot be performed without anesthesia deep enough. So, it is of very limited clinical significance to compare between with and without anesthesia. As we mentioned above, all the currently available GAs have been reported to produce neurotoxicity in developing brains. Therefore, from clinical perspective, it is more reasonable for us to compare different types of GAs, such as inhaled *versus* intravenous, to identify the one with least neurotoxicity, if there is one.

Another factor needs to be considered is that the primary diseases which require surgical treatment. It is evident that different diseases produce different effects on neurodevelopment.[9] So, it is equally important to restrict the types of diseases in the future trial.

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In summary, the causal relationship between early-life exposure to GAs and neurodevelopment impairment has not been proved with human evidence, which remains one of the most intensively investigated filed in our specialty. But considering the convincing results from massive preclinical studies, it may be the time for us, the anesthesiologists, to accept the concept that anesthesia is not completely reverse and it is highly like to produce a permanent effect in developing the brain. However, we should not dwell on whether GA is neurotoxic or not. No matter how toxic it could be, most of the surgeries cannot be performed without proper anesthesia, because the untreated pain caused much more harm to children and their developing brains. Instead, it is urgent for us to find out the least toxic GA among current available GAs. Like the surgeons, who never stop performing surgery in the fear of an ugly scar, instead, they are just trying their best to make it smaller. We, anesthesiologists, should not be demanding of the neurotoxicity of GAs on developing brain while ignoring the huge benefit provided by our excellent care.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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