

REVIEW

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Vitamin deficiency, a neglected risk factor for post-anesthesia complications: a systematic review

Ahmad Bagheri Moghaddam¹, Amene Raouf-Rahmati², Ahmad Nemati³, Shabnam Niroumand⁴, Ahmad Reza Mashreghi³, Mobin Gholami³ and Ramin Bahramizadeh Sajjadi^{1*}

Abstract

Background Some evidence highlights individuals lacking an adequate level of vitamins may experience heightened susceptibility to post-anesthesia complications. The current study summarized the previous evidence assessing the impact of deficient vitamin levels on complications and outcomes following anesthesia.

Methods A comprehensive search in scientific English databases was conducted from January 2000 to January 2024. The inclusion and exclusion criteria were applied, the full-texts were thoroughly analyzed, and the risk-of-bias was assessed.

Results A multitude of 1322 published articles were discovered based on search strategy and 14 eligible papers were enrolled. The mean age of patients was 39.3 years and the majority were male. Patients with vitamin B12 deficiency experienced both neurological and hematologic consequences post-anesthesia. Delirium was observed among patients lacking sufficient levels of vitamin D, and those deficient in vitamin K presented symptoms indicative of epidural hematoma. Post-anesthesia consequences were manifested with a delay, ranging from hours to days following the anesthesia procedure in vitamin K and B12 deficiency, while patients deficient in vitamin C and B1 experienced an acute onset of symptoms during surgery. Significantly, a notable proportion (42%) had pre-existing risk factors for vitamin deficiency prior to the surgery, while 35% of the risk-factors for vitamin deficiency were diagnosed after the surgery. There was a wide range of complete or partial recovery periods following surgical intervention, spanning over a few days up to several months according to the severity of symptoms.

Conclusions Based on the evidence from the reviewed studies, this study robustly suggests that serum vitamins level before surgery should be measured among patients who are at risk of vitamin deficiency or have some related clinical symptoms.

Keywords Anesthesia, Surgery, Vitamin deficiency, Anesthesia outcome, Post-anesthesia complication, Systematic review

*Correspondence:

Ramin Bahramizadeh Sajjadi
rbahrami477@yahoo.com

Full list of author information is available at the end of the article



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Background

Preoperative risk assessment is of great importance for the anesthesiologist in developing both a surgical procedure and a personalized and safe anesthesia procedure for patients undergoing surgery. Pre-anesthesia evaluation encompasses a comprehensive examination of the patient's health, including underlying disorders, physical health, cardiovascular and respiratory functions alongside other relevant systems, medication history, allergies, and various laboratory tests [1, 2]. By detecting any potential problems or abnormalities beforehand, appropriate steps can be taken to optimize the patient's condition before administering anesthesia. Complete blood count (CBC), electrolyte and creatinine levels, coagulation tests, etc. are applied as part of the laboratory screening tests [3]. Through preoperative assessments, informed decisions can be made regarding the choice between general anesthesia (GA) or local anesthesia, as well as determining the appropriate approach for induction of anesthesia before the surgical procedure.

Vitamin deficiency remains a global issue and over 2 billion people worldwide were found to lack adequate levels of vitamins and minerals according to data provided by the World Health Organization (WHO) [4]. In some developing countries or impoverished nations, severe vitamin deficiency is widespread as a result of food shortages and malnutrition [5]. While, this issue is largely absent in the general population in more affluent nations, where overall health standards are higher. However, it remains a concern for certain individuals who present specific behaviors, such as vegetarianism or alcoholism, and patients with conditions like celiac disease or those with a history of bariatric surgery [6].

The deficiency of vitamin levels can have some side effects after surgical outcomes, this might be more severe among various vitamins [7]. Moreover, some patients may be prone to developing a lack of vitamins following surgery or exposure to anesthetics, for instance, the use of nitrous oxide as an anesthetic has been linked to potential decreases in vitamin B12 levels [8]. In addition, as shown by Jensen et al. surgical stress can result in lower levels of vitamins such as vitamin D among patients undergoing elective surgeries [9]. On the other hand, several clinical trials have evaluated the beneficial effects of preoperative vitamin administration in patients with sufficient serum vitamin concentrations. Hung et al. have demonstrated that consuming vitamin C before undergoing a surgical procedure can alleviate the severity of postoperative pain [10]. Furthermore, a positive effect has emerged from a study demonstrating the advantages of preoperative supplementation with vitamin D in outcomes of cardiac surgeries [11]. Despite the fact that taking vitamins before surgery can be beneficial, it may not

be logical and cost effective to prescribe for all patients. In addition, routine vitamin screenings before surgery remain uncommon.

In this study, we aimed to review previous studies on how deficient vitamin levels may affect the complications and outcomes following anesthesia in patients who have undergone surgery for any reason. The period of our study extended from 2000 to 2024, because anesthesia techniques have evolved significantly since 2000.

Methods

Search strategy

The identification of relevant literature was carried out through a comprehensive search in the scientific English databases including PubMed, Web of Science, Science Direct, and Google Scholar from January 2000 to January 2024. The following combination of keywords with the recruitment of the Boolean operator "AND" to intersect different concepts and "OR" to encompass similar concepts were including (vitamin OR "vitamin deficiency") AND (anesthesia OR "pre-anesthetic" OR surgery OR "surgery outcome" OR "surgery complication" OR "post-anesthetic complication" OR "postoperative outcome" OR "postoperative complication"). Moreover, MeSH terms within PubMed were invoked to augment the quest.

Data extraction

The systematic data selection was in accordance with 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Data sets based on exclusion or inclusion criteria were extracted by two experienced writers who worked independently, RB-S and SN. In cases with no agreement, a thorough discussion involving a third reviewer, AR-R, was held until reaching a consensus. In the first step, the authors performed an assessment of the title/abstract of each citation followed by retrieving relevant full-text. Inclusion criterion was original relevant abstract and the parameters for exclusion were detailed in the PRISMA 2020 Flow Diagram (Fig. 1).

Quality assessment (risk-of-bias)

The Joanna Briggs Institute (JBI) critical appraisal checklist for case-report studies and JBI checklist for cohort studies were used to assess the quality of the included studies [12]. This case-report checklist provides a framework for writing a quality case report, including eight items. The items used for the assessment were as follows: (1) patient's demographic information, (2) patient's history, (3) patient's current clinical condition, (4) diagnostic and assessment methods and the results, (5) the treatment procedure and interventions, (6) post-intervention

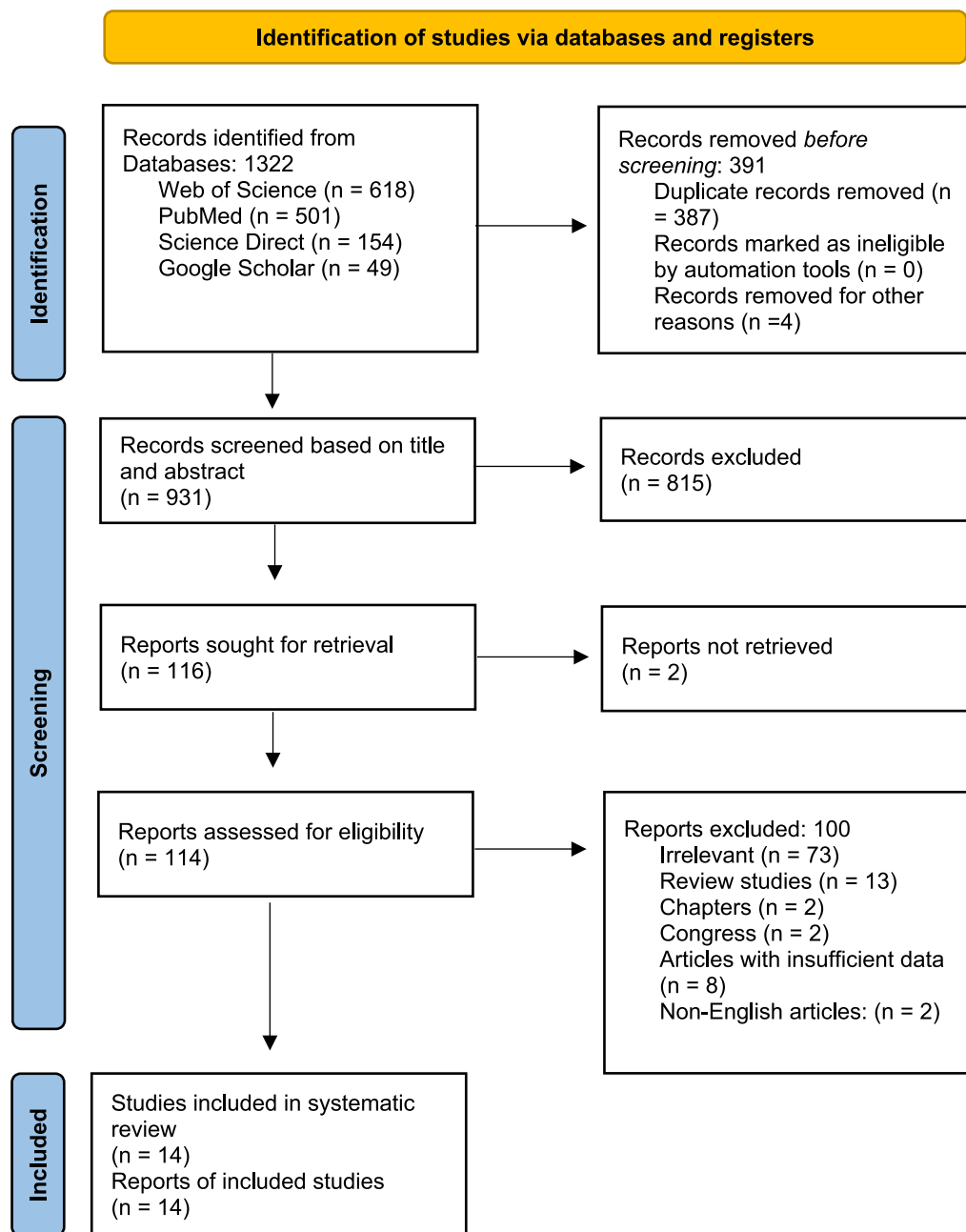


Fig. 1 Flow chart of the study selection process for the studies that confirmed the association between post-anesthesia complications and vitamin deficiencies based on PRISMA 2020

clinical condition, (7) adverse or unanticipated events and takeaway lessons, and (8) appropriate statistical analysis. According to the recommendations of the JBI's guidelines, each question was judged "yes" indicating a low risk of bias, "no" indicating a high risk of bias that negatively impacts the overall quality of the case reports, and "unclear" indicating an unclear or unknown risk of bias.

For the quality assessment of case-report studies, "Low," "Moderate," or "High," quality was rated for any study given <4 scores, 4–5 scores, and 6–7 scores, respectively. The cohort checklist provides 11 items generally regarding the population and two groups, the confounding factors, the validity, and reliability of exposure measured and outcomes, patient's follow-up process, and appropriate statistical analysis. For quality assessment

of retrospective studies, the mentioned scores were given <5 scores, 5–8 scores, and 9–11 scores, respectively. The quality assessment was independently performed by two researchers (AN and AM). In cases where there was no agreement in scoring, the third person (AB-M) assessed the articles.

Data synthesis

The requisite information obtained from each eligible study that met the inclusion criteria included the author's name, year of publication, study design, patient's demographic data (gender and age), anesthesia method, surgical procedure, pre- and post-anesthesia findings or adverse effects, onset time of consequences, risk factors for vitamin deficiency, laboratory and imaging results, therapy intervention or treatment, and outcomes.

Results

The process of study selection is depicted in Fig. 1 based on PRISMA 2020 Flow Diagrams. A total of 1322 records between 2000 and 2024 were discovered in databases and underwent a thorough examination. After eliminating 387 duplicate studies, an additional 815 publications were excluded based on title/abstract. In the next step, 114 reports were assessed for eligibility, and 14 studies including twelve case reports/series alongside two retrospective studies successfully met the criteria for inclusion.

Table 1 presents the detailed results of various factors related to the patients encompassed in this study. The mean age of patients was 39.3 years. Regarding the case studies, the majority of patients were male (85.7%), with only two cases of vitamin B12 deficiency being female [13, 14].

Among 92.8% of the patients (13/14), GA was administered, while complications from local anesthesia exclusively emerged in patients with vitamin K deficiency [15]. In a case report, one patient with an undiagnosed vitamin K deficiency developed a spinal epidural hematoma after the removal of an epidural catheter [16].

In approximately 78.5% of cases (11/14), symptoms manifested after delay, while three patients experienced acute onset of symptoms during surgery, two with vitamin C deficiency and one with vitamin B1 deficiency [17–19].

In three cases, patients displayed unstable vital signs, two cases were linked to vitamin C deficiency and one case to vitamin B12 deficiency [17–19], one patient with inadequate vitamin C experienced a cardiac arrest during surgery [17]. Patients diagnosed with epidural hematoma as a result of vitamin K deficiency experienced a decrease in limb strength [15, 16]. Among nine patients with B12 deficiency, three experienced

impaired cognition, while others exhibited impaired motor function. All of them reported sensory complications including pain, proprioception, or vibration sense [13, 14, 20–24]. In relation to vitamin D deficiency, patients were found to be more susceptible to delirium [25, 26].

Nearly half of the patients (6/14) had preexisting risk factors for vitamin deficiency. Three patients had restricted vitamin supplies through their diet and malnourishment [17, 18], and two patients who suffered from gastrointestinal disorders resulting in malabsorption leading to vitamin K deficiency [15, 16], and a patient with diabetes.

Out of nine cases of vitamin B12 deficiency, 55% had anemia and 77% had increased MCV, while folate serum levels were normal in all patients with B12 deficiency. MRI abnormalities were found in the posterior column of the spine in all of the cases with B12 deficiency.

The recovery of patients with vitamin deficiency after treatment revealed a wide range postoperative recovery periods spanning from a few days to several months.

Discussion

The findings elucidate that out of 14 patients examined in case reports, the complications were predominantly observed in males. Both cases of vitamin C deficiency occurred in children aged 6 and 13 years [17, 18], while cases involving vitamin K deficiency affected elderly individuals 65 and 72 years [15, 16]. Besides, two case-control studies examined the role of vitamin D deficiency in delirium after surgery, specifically among patients older than 55 and 65 years [17, 25]. Our study revealed that depending on the severity of vitamin deficiency, the onset of complications varies, from emerging during the procedure to weeks post-surgery. Moreover, it was observed that the occurrence of most complications was noted alongside the administration of general anesthesia. GA has the potential to induce hypotension in individuals suffering from particular types of vitamin deficiencies, resulting from pulmonary hypertension or heart failure [17–19]. This study highlighted that patients with vitamin D deficiency are more susceptible to experiencing postoperative delirium. Epidural hematoma subsequent to local anesthesia was identified as the most prevalent complication associated with vitamin K deficiency. All patients afflicted with neurological issues resulting from vitamin B12 deficiency underwent nitrous oxide anesthesia. Regarding recovery of individuals, nine achieved complete improvement, while one case K deficiency, one case vitamin c deficiency, and three cases of cobalamin deficiency did not improve completely [14, 16, 21, 23].

Table 1 Summarized of studies evaluating the role of vitamin deficiency and possible post anesthesia consequences

Authors name	Cases Gender/Age	Type of vitamin deficiency	Anesthetic method and Medication	Type of surgery	Pre-anesthesia findings	Onset of symptoms	Post-anesthesia complications	Post-anesthesia laboratory and radiographic findings	Symptoms related to vitamin deficiency	Treatment	Outcome	Overall Quality appraisal based on JBI checklist
Kshirsagar et al. [19]	M/13	B1	GA with Propofol, Atracurium, and Sevoflurane	Skin grafting	Electric burns over the right arm, right axillary region, and right and left foot in 2013	During surgery	Tachycardia and dropped SpO2 due to acute decompensated heart failure	Echocardiography showed Left ventricular hypokinesia with ejection fraction of 20% and MR/TR, Chest X Ray showed pulmonary edema	Weight loss, impaired wound healing, decreased appetite and impaired concentration	100 mg IV Thiamine for 5 days + treatment of heart failure	Complete improvement after 4 days	High
Ahn and Brown [20]	Male in early forties	B12	GA with Nitrous oxide	Femoral-peroneal bypass+below-knee amputation	Diabetes, Hyperhomocysteinemia, left hemisphere cortical stroke from carotid dissection with neurologic consequences	postoperative	Impaired reflex of lower limb, impaired sensation, general weakness and ataxia	Normal Hb and MCV, low serum B12: 140 ng/L (200–650 ng/L), High folate 200 µ/L (≥35 µg/L); high homocysteine, 111 µmol/L (≤13 µmol/L)	Neurological complications and impaired wound healing	At first week: 1 mg cyanocobalamin + 50 mg vitamin B6 + 2 mg folic every day. After first week: 0.1 mg cyanocobalamin, 25 mg vitamin B6, and 1 mg 2 mg folic per day + rehabilitation treatment	Complete improvement of muscle strength after 1-month, partial improvement of sensory and proprioception after 9 months	High
Maré et al. [21]	M/69	B12	GA with Nitrous oxide	Prosthetic adenoma	NM	2 weeks post-operative	Impaired reflex of lower limb, ataxia, impaired sensation of proprioception, flaccid paraplegia, urine retention, fecal incontinence, confusion, disorientation, impaired memory	Lower than normal Hb, increased MCV, low serum B12 (812); 37 pmol/L (130–700 ng/L), normal folate level: 30 nmol/L (5–30 nmol/L), Anti intrinsic factor was detected in serum, Spinal MRI showed T2-weighted hypersignal part in posterior and lateral column	Neurological complications with diagnosis of pernicious anemia	First 5 days: 1 mg IM cyanocobalamin/daily For next six months: 5 mg IM cyanocobalamin/daily For second sixth month: 5 mg IM cyanocobalamin/ weekly	Partial improvement after 6 months: disorientation and confusion completely diminished; other symptoms recovered partially	High

Table 1 (continued)

Authors name	Cases Gender/Age	Type of vitamin deficiency	Anesthetic method and Medication	Type of surgery	Pre-anesthesia findings	Onset of symptoms	Post-anesthesia complications	Post-anesthesia laboratory and radiographic findings	Symptoms related to vitamin deficiency	Treatment	Outcome	Overall Quality appraisal based on JBI checklist
Singer et al. [13]	F/27	B12	GA with nitrous oxide	Dental procedure	No significant past medical history	2 months postoperative	Impaired reflex of lower limb, normal cognition, paresthesia, impaired sensation of proprioception and vibration, wide gait, ataxia	Lower than normal Hb, normal MCV, serum B12: 290 pg/mL (211–911 pg/mL), and folate level: 12.7 ng/mL (> 5 ng/mL), high homocysteine: 17 m mol/L (0–13 m mol/L), Anti intrinsic factor was detected in serum, Spinal MRI showed T2-weighted patchy enhancement in posterior column	Neurological complications with diagnosis of pernicious anemia	For 10 months: 1 mg vit B12 IM/ monthly	Complete recovery after 10 months. MRI was normalized after 1 month	High
Safari et al. [22]	M/50	B12	GA with nitrous oxide	Tympanoplasty	The patient's background did not reveal pre-existing diabetes mellitus, alcohol consumption, vegetarian food preference, gastrointestinal symptoms, or previous neurological disorder	10 days post-operative	Ataxia, paresthesia, anorexia, depressed mood, normal reflex, normal cognition, impaired sensation of proprioception and vibration	Lower than normal Hb, increased MCV, lower than normal serum level of B12: 101 (the unit of measurement has not been specified), hypersegmented neutrophil, Anti intrinsic factor was detected in serum, Spinal MRI showed T2-weighted hypersignal part in posterior column	Neurological complications, anorexia with diagnosis of pernicious anemia	For first week: 1 mg IM cyanocobalamin/daily For next 4 weeks: 1 mg IM cyanocobalamin/weekly After that 1 mg IM cyanocobalamin was continued monthly	Complete improvement after 4 weeks	High

Table 1 (continued)

Authors name	Cases Gender/Age	Type of vitamin deficiency	Anesthetic method and Medication	Type of surgery	Pre-anesthesia findings	Onset of symptoms	Post-anesthesia complications	Post-anesthesia laboratory and radiographic findings	Symptoms related to vitamin deficiency	Treatment	Outcome	Overall Quality appraisal based on JBI checklist
Ilinczyk et al. [23]	M/57	B12	GA with nitrous oxide	Extra-intracranial artery bypass surgery	NM	2 months postoperative	Impaired reflex of lower limb, ataxia, impaired sensation of proprioception, decreased force of limbs, normal cognition	Normal Hb and folate level, increased MCV, low serum B12: 135 pmol/L (146 ± 518 pmol/L), abnormal Schilling test, Spinal MRI showed T2-weighted hyper-signal part in posterior column, while it was hypo signal in T1	Neurological and dermal complications: glossitis, fissures in both angles of the mouth with diagnosis malabsorption of B12	First 5 days: 1 mg IM cyanocobalamin/daily	Complete recovery after 3 weeks. MRI was normalized after 1 month	High
	M/52	B12	GA with nitrous oxide	Cholecystectomy	NM	7 days post-operative	Paresthesia, weakness, Impaired reflex of lower limb, ataxia, decreased force of limbs, normal cognition	Normal Hb, increased MCV, low serum B12, decreased folate level, abnormal Schilling test	Neurological and dermal complications: glossitis, fissures in both angles of the mouth, abdominal pain with diagnosis malabsorption of B12	First 5 days: 1 mg IM cyanocobalamin/daily	Complete recovery of muscle strength after 1 week but other symptoms were resolved partially, MRI was normalized after 3 weeks	High

Table 1 (continued)

Authors name	Cases Gender/Age	Type of vitamin deficiency	Anesthetic method and Medication	Type of surgery	Pre-anesthesia findings	Onset of symptoms	Post-anesthesia complications	Post-anesthesia laboratory and radiographic findings	Symptoms related to vitamin deficiency	Treatment	Outcome	Overall Quality appraisal based on JBI checklist
Gursoy et al. [14]	F/58	B12	GA with nitrous oxide	Thyroidectomy	NM	6 weeks post-operative	Impaired sense proprioception and vibration, Impaired reflex of lower limb, ataxia, decreased force of limbs, normal cognition	Normal Hb and folate levels, increased MCV low serum B12: 143 g/mL (211 pg/mL), Spinal MRI showed T2-weighted hypersignal part in posterior column	Neurological complications	First 2 weeks: 1 mg IM cyanocobalamin/daily After that: 1 mg IM weekly	Complete recovery of muscle strength and MRI findings, but vibratory sense resolved partially	High
Feimet et al. [24]	M/8 months	B12	GA with nitrous oxide and isoflurane	Laparoscopic orchiopexy	Neurodevelopmental delay, impaired growth Mother had pernicious anemia	6 days after surgery	Fever, lethargy, paleness, impaired movements	Pancytopenia, increased MCV, low serum B12: lower than normal level 20 pg/mL (200–950 pg/mL), increased lactic dehydrogenase level, folate level was normal, hyper level of homocysteine 120 µmol/L (12–9.6 µmol/L)	Neurological complications and diet without vitamin supplementation	IM hydroxycobalamin	Complete recovery after 4 months	High
Zavaleta et al. [18]	M/13	C	GA with fentanyl, propofol, and succinylcholine	Esophagogastroduodenoscopy (EDG) and colonoscopy	ASD, Malnutrition, melena, anemia, loss of appetite, gingivitis in lower limbs, hematemesis	During surgery	Significant decreased of blood pressure	Lower than normal Hb, low Vitamin C level: <5 µmol/L (23–114 µmol/L)	ASD with malnutrition and diet without vitamin supplementation	First week: IV Vitamin C three times a day	Complete recovery after 7 days	High

Table 1 (continued)

Authors name	Cases Gender/Age	Type of vitamin deficiency	Anesthetic method and Medication	Type of surgery	Pre-anesthesia findings	Onset of symptoms	Post-anesthesia complications	Post-anesthesia laboratory and radiographic findings	Symptoms related to vitamin deficiency	Treatment	Outcome	Overall Quality appraisal based on JBI checklist
Quinn et al. [17]	M/6	C	GA	EDG for placing a bridled nasogastric tube	ASD Malnutrition	During surgery	cardiac arrest due to pulmonary hypertensive crisis during GA	Lower than normal Hb with iron deficiency, low Vitamin C level < 0.1 mg/dL, (0.4–2 mg/dL), low thiamine level: 55 nmol/L (70–180 nmol/L), low Vitamin A level 15 mcg/dL (19–77 mcg/dL), low vitamin D level < 3.5 ng/mL (30–96 ng/mL). Echocardiogram revealed pulmonary arterial hypertension (PAH) and hypertrophy of right ventricle	ASD with malnutrition and diet without vitamin supplementation, mucositis;	Multivitamin, sildenafil, multivitamin, zinc, and ferrous sulfate	Partial improvement after 6 weeks including persistent right ventricular hypertrophy without PAH	High
Rawley et al. [15]	M/72	K	LA	Placing Thoracic epidural catheter	Colo-vesicular fistula, chronic obstructive lung disease, prolonged aPTT (41 s) (normal range was less than 35 s)	32 h postoperative	Cramp pain between scapula, dyspnea, decreased force of four limbs	Prolonged PT (16.4 s), prolonged aPTT (47 s), lupus anticoagulant antibody was detected in serum. CT revealed hyperdensity in spinal canal	Lupus anticoagulant antibody with coagulopathy	Removal of the epidural catheter. Supplementation of Vitamin K	Complete improvement	High
Ladha et al. [16]	M/65	K	GA with fentanyl and propofol	Removal of Thoracic epidural catheter	Gastric cancer, anemia, normal coagulation tests,	24 h postoperative	Severe back pain, acute paraplegia	Prolonged INR and PTT MRI revealed an epidural hematoma	Taking enoxaparin, no intake of food for some days, coagulopathy	Surgery for decompression of hematoma and injection of vitamin K	Partial improvement of paraplegia after 1 year	High
Tumer et al. [25]	212 adult patients above 65 years	D	GA	Coronary artery bypass graft (CABG)		Postoperative	After surgery delirium was significantly more common among patients with lower level of 25-OHD concentration	25OHD serum level lower than 25 ng/mL				High

Table 1 (continued)

Authors name	Cases Gender/Age	Type of vitamin deficiency	Anesthetic method and Medication	Type of surgery	Pre-anesthesia findings	Onset of symptoms	Post-anesthesia complications	Post-anesthesia laboratory and radiographic findings	Symptoms related to vitamin deficiency	Treatment	Outcome	Overall Quality appraisal based on JBI checklist
Qiu et al. [26]	632 patients with the mean age 55–61 years	D	GA	Patient admitted to ICU after non-cardiac and non-neurosurgical operations		Postoperative	Patients with lower preoperative serum 25-OHD levels were more susceptible to delirium (1.4time higher risk of delirium per 10 ng/mL decrease in 25-OHD concentrations)	25OHD serum level lower than 30 ng/mL				High

GA: General anesthesia; LA: Local anesthesia; NM: Not Mentioned; MR: Mitral regurgitation; TR: Tricuspid regurgitation; IV: Intravenous; IM: Intramuscular; MCV: Mean corpuscular volume; Hb: Hemoglobin; MRI: Magnetic resonance imaging; ASD: Autism spectrum disorder; EDG: Esophagogastroduodenoscopy; PAH: pulmonary arterial hypertension; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; PTT: Partial thromboplastin time; 25OHD: 25 hydroxy vitamin D3 (cholecalciferol); ICU: Intensive Care Unit

Vitamin B1 (thiamine)

Thiamine and its active form, thiamine pyrophosphate (TPP), serve as a co-factor in the processes of both the citric acid cycle and the pentose phosphate pathway. Furthermore, TPP plays a major role in facilitating the aerobic metabolism of glucose for energy production [27]. Insufficient or deficient thiamine can manifest in various forms, ranging from tiredness and loss of appetite in mild conditions to wet beriberi, which predominantly affects the cardiovascular system, or dry beriberi, which predominantly affects the neurovascular system in severe conditions [28]. Notably, these symptoms often afflict individuals who have had a history of chronic alcoholism, prolonged malnutrition, and utilization of medications that interfere with thiamine metabolism [27, 28]. In the current review study, only one demonstrated a clear association between vitamin B1 deficiency and some postoperative complications. A 13-year-old boy who underwent skin grafting under general anesthesia with propofol, atracurium, and sevoflurane, displayed various manifestations including tachycardia and dropped percentage of saturation of Oxygen (SpO₂) resulting from acute decompensated heart failure, loss of weight, impaired wound healing, decreased appetite and impaired concentration after surgery. The young patient had complete improvement within 4 days by receiving treatment consisting of 100 mg intravenous thiamine for 5 days as well as therapy for his heart failure [19]. According to the author's report, a vegetarian diet is identified as a probable risk factor for thiamine deficiency which has been observed during surgical procedures leading to acute decompensated heart failure [19]; however, vegetarian diet is a rare reason for thiamine deficiency.

Vitamin B12 (cobalamin)

Cobalamin is a water-soluble vitamin responsible for the production of red blood cells and proper neurological function. It acts as a vital coenzyme in the synthesis of DNA and RNA while also participating in the metabolism of hormones, proteins, and fatty acids. Inadequate cobalamin levels can result in various symptoms, such as megaloblastic anemia, fatigue, reduced appetite, and neuropsychiatric complications [29, 30]. Although clinical B12 deficiency is relatively uncommon, subclinical deficiency affects a considerable range between 2.5 and 26% of the general population [31]. The elderly are particularly susceptible to developing vitamin B12 deficiency which has been associated with earlier onset, more progressive, and more severe dementia [32]. Certain individuals with predisposing factors, such as older age, ongoing use of medications that disrupt cobalamin metabolism, pernicious anemia, diabetes, vegans,

pregnant or breastfeeding women, and those with malabsorption issues in the gastrointestinal tract bear a higher risk of experiencing cobalamin deficiency [29, 31]. The administration of nitrous oxide as a form of anesthetic drug in anesthesia procedures is an important but overlooked risk factor for the manifestation of vitamin B12 deficiency after the surgery. Nitrous oxide oxidizes Co(I) in vitamin B12 to Co(II) and, therefore, inactivates vitamin B12 and interferes with its normal functions within the body [33]. This impairment in B12 activity can result in serious clinical consequences such as megaloblastic anemia in the bone marrow and neurological-subacute combined degeneration of the spinal cord, as well as pernicious anemia. The present study found ten related articles exploring the possible consequences of anesthesia on patients with vitamin B12 deficiency. Remarkably, all cases of anesthesia-related complications occurred exclusively following the induction of nitric oxide [13, 14, 20–24]. Among patients with vitamin B12 deficiency, it was observed that symptoms were manifested with a delay, ranging from 6 days to 6 weeks with a mean onset of 29 days [13, 14, 20–23].

Among the patients who were diagnosed with B12 deficiency, three individuals suffered from impaired cognition, six cases exhibited impaired motor function, and all of them experienced sensory complications including pain, proprioception issues, or disrupted vibration sense [13, 14, 20–24]. One of those suffered from diabetes [20]. Five patients presented with previously undiagnosed disorders, which were subsequently identified following general anesthesia. Among these cases, three were diagnosed with pernicious [13, 20, 21] and two others exhibited malabsorption issues [23]. It was noted that the majority of individuals afflicted with vitamin B12 deficiency were males (7 out of 9 cases). The youngest patient was an infant merely 8 months who underwent laparoscopic orchiopey under general anesthesia with nitrous oxide and isoflurane. Following the surgery, the infant experienced neurological and hematologic complications due to a serum cobalamin concentration below 20 pg/mL (normal range: 200–950 pg/mL), although folate levels remained within normal parameters. It appears that the deficiency was exacerbated by the induction of nitric oxide. Nonetheless, all patients recovered completely after undergoing intramuscular hydroxyl cobalamin therapy [24]. Out of nine cases of vitamin B12 deficiency, 55% displayed anemia, 77% showed increased MCV, while folate serum levels remained normal in all patients. MRI abnormalities were detected in the posterior column of the spine in all of the cases with B12 deficiency. Interestingly, in a case with high homocysteine levels and MRI findings relevant to cobalamin deficiency, the level of cobalamin was within the normal range [13].

In agreement with our study, in a systematic review exploring the effects of nitrous oxide on neurologic complications, it was discovered that the majority of cases demonstrated an underlying gastrointestinal disorder characterized by cobalamin deficiency that was further exacerbated following the administration of anesthesia [34]. Moreover, remarkable investigations divulged that individuals who abuse nitrous oxide or are occupationally exposed to it often experience impaired vitamin B12 metabolic status [35–40]. These observations strongly suggest that patients with low vitamin B12 levels are potentially at heightened risk for adverse effects when subjected to nitrous oxide during anesthesia. Therefore, it is crucial to restrict nitrous oxide as an anesthetic drug for patients suspected of cobalamin deficiency.

Vitamin C (ascorbic acid)

Ascorbic acid, a water-soluble vitamin, is vital for various bodily functions, such as collagen synthesis, the production of certain hormones and neurotransmitters, the metabolism of amino acids and vitamins, and the detoxification of toxic substances [41]. Deficiency in vitamin C has been extensively documented among elderly people, alcoholics, those with mental illnesses, and individuals following restrictive diets [42]. The available evidence indicates that vitamin C deficiency is common among low- and middle-income nations and uncommon in high-income countries [42]. Prolonged and severe vitamin C deficiency results in scurvy, a clinical syndrome that can be fatal if left untreated [42]. In our study, two researchers separately reported complications due to vitamin C deficiency in 13- and 6-year-old males with autism spectrum disorders undergoing esophagogastroduodenoscopy with general anesthesia [17, 18]. Both patients exhibited malnutrition and followed a diet without vitamin C supplementation, resulting in vitamin C levels $<5 \mu\text{mol/L}$ (normal range: $23\text{--}114 \mu\text{mol/L}$) and $<0.1 \text{ mg/dL}$ (normal range: $0.4\text{--}2 \text{ mg/dL}$). Both patients also presented lower than normal hemoglobin concentrations. However, the case of the 6 years in addition to vitamin C deficiency involved a combination of other vitamin deficiencies, including thiamine at 55 nmol/L ($70\text{--}180 \text{ nmol/L}$), vitamin A at 15 mcg/dL ($19\text{--}77 \text{ mcg/dL}$), and vitamin D level $<3.5 \text{ ng/mL}$ ($30\text{--}96 \text{ ng/mL}$). This case afflicted cardiac arrest due to a pulmonary hypertensive crisis during anesthesia. In this intricate case, the patient received multivitamins, sildenafil, zinc, and ferrous sulfate for treatment and developed partial improvement after 6 weeks [17]. Another case who exhibited a decline in blood pressure following anesthesia was treated completely within 7 days by receiving intravenous vitamin C three times a day for 5 weeks. In contrast, a 2020 systematic review and meta-analysis of observational studies, demonstrated

a correlation between serum vitamin C levels and hypertension. According to this study, hypertensive subjects showed significantly $15.13 \mu\text{mol/L}$ lower concentration of serum vitamin C compared to those classified as normotensive ($P=0.001$). This study concluded that serum vitamin C has an inverse significant relationship with both diastolic systolic) and systolic blood pressure (both $P<0.00001$) [43]. Vitamin C deficiency has a significant impact on the development of pulmonary arterial hypertension through mechanisms, such as impairments in nitric oxide production, turnover of reactive oxygen species, and oxygen sensing. In the presence of sufficient vitamin C, nitric oxide synthase converts L-arginine into L-citrulline to the generation of nitric oxide [44]. In a low level of vitamin C condition, due to insufficient generation of endogenous endothelial nitric oxide, the increased vascular tone in the pulmonary arteries and subsequently development of pulmonary arterial hypertension can result. Duvall et al. reported the association between pulmonary hypertension, scurvy, and vitamin deficiencies in an autistic child [44]. Such association was supported repeatedly by other research [18, 45, 46]. Furthermore, vitamin C due to its anti-oxygen species properties has a protective effect in pulmonary arterial hypertension [47]. Given these findings, it is imperative to screen individuals who are susceptible to vitamin C deficiency before undergoing anesthesia.

Vitamin D

A sufficient supply of vitamin D is crucial in terms of appropriate brain development and nervous cell functions [48]. Low concentrations of serum 25-hydroxy vitamin D [25(OH)D] have been linked to various cognitive impairments, such as dementia, cognitive impairment, and delirium among hospitalized patients [49, 50]. According to a review study assessing the prevalence of vitamin D deficiency, one out of every five Asian individuals displayed significant vitamin D deficiency. This trend was more prevalent amongst the elderly people, raising concerns regarding public health [51]. A pooled analysis involving 7.9 million participants worldwide revealed that the rates of vitamin D deficiency ($<30 \text{ nmol/L}$) and insufficiency ($30\text{--}50 \text{ nmol/L}$) were 15.7% and 32.2%, respectively, between 2000 and 2022 [52]. A study highlighted that preoperative vitamin D deficiency is associated with an increased rate of mortality of patients (21.5% vs 6.3%, $P=0.011$) in the first year after geriatric hip fracture surgery [53]. Based on the present systematic search, two retrospective studies [25, 26] have reported that vitamin D deficiency especially in elderly adults can increase the risk of experiencing postoperative delirium. The study populations were patients aged over 55 and 65 years with serum vitamin D levels lower

than 25 and 30 ng/mL who underwent general anesthesia due to coronary artery bypass graft and patients admitted to ICU after non-cardiac and non-neurosurgical surgeries. Both studies concluded that the likelihood of developing postoperative delirium is significantly more prevalent among patients with lower vitamin D concentrations. One of two studies found a 1.4 times higher risk of delirium with every 10 ng/mL decrease in vitamin D concentrations [26]. The two studies asserted delirium due to preoperative vitamin D deficiency occurs more frequently within the initial 2 days following the surgical procedure [25, 26]. The pathophysiologic cause of delirium is not well understood, but a 2022 meta-analysis involving 2673 patients demonstrated that preoperative vitamin D deficiency increased the risk of postoperative delirium and cognitive dysfunction ($P < 0.01$) [54]. Such evidence was confirmed by a subsequent meta-analysis carried out by Fu et al. among hospitalized patients with vitamin D deficiency [49]. Regarding the neuroprotective role of vitamin D in influencing neuromediator synthesis and preventing oxidative damage to nervous systems and protecting neurons, the impact of insufficient vitamin D levels in mental health conditions including delirium and Alzheimer can be justified [48, 55]. Vitamin D also mediates the inflammatory processes within the nervous systems under certain circumstances and also impacts systemic inflammation resulting in various pathological manifestations, such as delirium [56]. Hence, we suggest that surgeons and anesthesiologists consider the level of vitamin D in elderly adults as a means of reducing the incidence rate of delirium following surgery.

Vitamin K

Vitamin K is a fat-soluble derivative that is involved in some physiological processes including bone metabolism, blood clotting, and cardiovascular health. It serves as a co-factor in facilitating the γ -carboxylation of glutamic acid, a posttranslational step in the synthesis of clotting factors II, VII, IX, and X as well as prothrombin, osteocalcin, anticoagulants C, S and Z [57]. Vitamin K deficiency may be commonly observed in typically healthy adults ranging from 8 to 31% [58]. The significant symptoms associated with this deficiency contribute to bleeding including spontaneous cutaneous purpura bleeding, epistaxis bleeding, gastrointestinal bleeding, genitourinary bleeding, and gingival bleeding [59]. Although vitamin K deficiency is not frequently observed in adults, it can manifest as a result of several reasons: (a) insufficient content of vitamin K in the diet, (b) pathological conditions, such as liver disorders, malignancies, malabsorption disorders, and bariatric surgical intervention, and (c) pharmacotherapy mainly coumarin-based anticoagulants [60–62]. Increased prothrombin time (PTT) was

observed across all patients exhibiting deficient amounts of vitamin K [15, 16]. On average, the presentation of epidural hematoma was documented 28 h post-anesthesia in patients afflicted with vitamin K deficiency [15, 16], underscoring the importance of addressing insufficient levels of vitamin K in individuals with multiple risk factors to prevent hemostatic complications. Subsequent to the surgery, both patients experienced symptoms including cramp pain, decreased force of four limbs, acute paraplegia, and epidural hematoma emerging above 24 h after the surgery. Eventually, a combination of interventions including vitamin K supplementation, surgery for decompression of hematoma, and removal of the epidural catheter lead to complete or partial improvement.

Limitations and weaknesses

The reliance on English-language publications and the exclusion of grey literature may have introduced publication bias and led to an incomplete representation of the available evidence. The study predominantly highlights specific vitamins (B12, D, K, C, B1) while potentially overlooking other nutritional deficiencies that could impact anesthesia outcomes. Furthermore, confounding factors such as medication use, socioeconomic status and lifestyle choices may not have been adequately controlled for, potentially influencing observed outcomes. In addition, due to the small number of previous studies identified, a meta-analysis could not be conducted. This limitation restricts the ability to perform a more robust statistical synthesis of the data, which would have allowed for a comprehensive evaluation of the relationships between vitamin deficiencies and post-anesthesia complications. Instead, the analysis relied on simple counting and calculation of frequency and mean values for each variable, which may not adequately capture the complexity of the associations or provide a nuanced understanding of the impact of vitamin deficiencies on patient outcomes. This approach may overlook important interactions and variations that could emerge from a more detailed statistical analysis, further limiting the depth of insights gained from the study.

Conclusion

Based on the evidence from the reviewed studies, vitamin deficiency can be considered a neglected risk factor for post-anesthesia complications. The main finding of this study is a potential impairment of vitamin B12 functioning resulting in vitamin B12 deficiency following general anesthesia under nitrous oxide. This study indicates that patients with vitamin K deficiency are at a higher risk of facing post-anesthesia consequences after receiving local anesthesia, so central blocks should be avoided in patients with abnormal PTT. We suggest that

before surgery vitamin serum levels should be evaluated in patients who display susceptibility towards vitamin deficiency or exhibit clinical signs of vitamin deficiency. In the event that a deficiency is detected, it becomes essential to implement appropriate measures for vitamin supplementation and modify the anesthesia procedure accordingly.

Supplementary Information

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Supplementary Material 1.

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Author contributions

AN, AR-R, RB-S, AM, AB-M and SN participated in collecting and examining the data. RB-S, AR-R, MG contributed to writing the manuscript and creating figures. RB-S and AB-M collaborated on designing the study.

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Declarations

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Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

Author details

¹Department of Anesthesiology and Critical Care, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ²Immunology Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ³MD, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ⁴Department of Community and Family Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

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