Original Article

Thiamine for Prevention of Postoperative Delirium in Patients Undergoing Gastrointestinal Surgery: A Randomized Clinical Trial

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ABSTRACT

Objective: Postoperative delirium is a common complication after gastrointestinal surgery that is associated with adverse outcomes. Thiamine is an essential cofactor for the glycolysis, oxidative metabolism, production of neurotransmitters in the crebs cycle. In this study, efficacy of thiamine was assessed as a preventive strategy of delirium in patients undergoing gastrointestinal surgery. **Methods:** In this randomized clinical trial, 96 adult patients admitted to the intensive care unit (ICU) following gastrointestinal surgery were included. Patients were allocated to receive either 200 mg intravenous thiamine daily or an equal volume of 0.9% saline for 3 days. Delirium was evaluated twice daily based on the confusion assessment method-ICU. The incidence of postoperative delirium was considered as the primary outcome, and total analgesic use and ventilation days has been defined as secondary outcomes of the study. **Findings:** The incidence rate of delirium was significantly lower in the thiamine group than the placebo group on the first day (8.3% vs. 25%; Odds ratio: 0.27 [95% confidence interval (CI): 0.08–0.92]; $P = 0.026$) and on the second day (4.2% vs. 20.8%; or: 0.16 [95% CI: 0.03–0.81]; $P = 0.014$). No adverse effect related to thiamine was detected during the study course. **Conclusion:** Study results suggest that thiamine is a safe option for the prevention of postoperative delirium in patients after gastrointestinal surgery.

KEYWORDS: *Delirium, gastrointestinal surgery, Thiamine*

INTRODUCTION

Delirium is a neuropsychiatric disorder characterized by acute onset of confusion, alteration in consciousness, fluctuating attention, and cognition disturbance.[1-3] The incidence of delirium was high and was reported in up to 80% of patients during intensive care unit (ICU) stay.[4] Delirium is associated with adverse outcomes, including higher mortality, prolonged duration of mechanical ventilation, higher ICU and hospital length of stay, and increased medical costs.[4-6] It is estimated that each day of delirium results in 10% increase in the relative risk of death.[4]

Delirium is a common neurobehavioral complication after major surgeries,[7] and the incidence rate is estimated as 36.8% in postoperative patients.[8,9] Considering burden prevalence of delirium, applying effective preventive strategies, especially in susceptible patients is essential.[10] Haloperidol and second-generation antipsychotics are the most commonly used pharmacological agents for prevention and treatment of delirium.[1,9] Unfortunately, antipsychotics can cause severe adverse effects such as metabolic disorders, cardiovascular events, and neuroleptic malignant syndrome.[9,10,11]

Thiamine is water-soluble vitamin essential for mitochondrial and cellular functions, which acts as cofactor for the pyruvate dehydrogenase complex (PDH) and for α-ketoglutarate dehydrogenase (α-KGDH). α-KGDH is a key enzyme in the synthesis and production of neurotransmitters and glutathione peroxidase.[12,13] Thiamine is essential for the mitochondrial synthesis of ATP.[14] Reduction of ATP in the brain leads to

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production of toxic metabolites that can be associated with hallucination, delusion, and delirium.[15] Thiamine deficiency was reported in 20% of patients with sepsis in ICU and 25% of patients after gastrectomy.[12,16,17] Although there are some useful agents for the treatment of delirium, there is no standard approach to prevent delirium in the postoperative patients.[18,19]

According to the several mechanisms that have been defined for the delirium also thiamine has important roles in oxidative metabolism, production of ATP and neurotransmitters, and reducing neuroinflammation. Thiamine is suggested as an option for prevention of postoperative delirium. No study has evaluated the effect of thiamine on prevention of postoperative delirium yet.

METHODS

This randomized, double-blind, placebo-controlled, clinical trial (ID: IRCT20190224042815N1) was conducted from March 2019 to November 2019 in general ICU of Imam Khomeini hospital, a tertiary referral teaching hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran. The institutional review boards and the ethics committee of Tehran University of Medical sciences approved this study with the code number: IR.TUMS. IPS.REC.1397.141.

The sample size of this pilot study (48 patients in each group) was calculated by considering $\alpha = 0.05$ and 80% power ($1-\beta = 0.8$). Because no data were available regarding the efficacy of thiamine in the prevention or treatment of delirium, data from the other studies were used for the sample size calculation.[20]

All patients over 18 years of age admitted in the ICU after gastrointestinal surgery were eligible to enter the study. Patients with a previous history of any neuropsychiatric disorder, severe renal impairment (glomerular filtration rate ≤ 30 mL/min/1.73 m^2), severe liver impairment (Child–Pugh C), substance or alcohol abuse, diabetic ketoacidosis, and delirious patients at the time of ICU admission were excluded. Furthermore, demographic and clinical data, duration of anesthesia, time of recovery, drugs, mechanical ventilation, Acute physiology and Chronic Health Evaluation II score at admission, and daily sequential organ failure assessment score were recorded.

Enrolled patients were randomized to receive either 200 mg of intravenous (IV) thiamine daily or an equal volume of 0.9% saline for 3 days based on the permuted-block randomization method. The randomization scheme consisting of twenty-four blocks, and each block contains four patients in random order.

A thiamine and placebo with similar color and appearance were prepared and assigned by the pharmacy department. A physician out of the research team was responsible for assessment of delirium. Therefore, patients and researchers were not aware of the allocation sequence.

The primary outcome of study was the incidence of postoperative delirium. Confusion assessment method (CAM-ICU) scale was applied for detection of delirium. At first, variations in the level of consciousness over time were evaluated according to the Richmond Agitation–Sedation Scale. Agitation was rated from 0 to +4.

In nonalert patients, the rate of sedation level scored based on the duration of eye contact ($-1--3$). Patients with no eye opening following verbal stimulation (recorded as -4 or -5) were not included.[21]

The CAM-ICU includes four features: (1) a change in mental status from baseline, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. Delirium was diagnosed if the patient was positive for both 1 and 2 features and either features 3 or 4.[22]

In this study, a validated Persian version of CAM-ICU was considered for assessment of delirium.[23] During the study period, sedation and delirium status for each patient were assessed every 12 h.

Analgesic-based sedation (analgosedation) was applied protocol in the ICU. Based on this protocol, opioid analgesics including IV fentanyl, morphine, or methadone was used for sedation. The mean dose of analgesic was calculated based on the morphine equivalent. Haloperidol was considered for any patient who experienced delirium.

Any new episode of flashing, pruritus, diaphoresis, nausea, and pharyngeal edema during the study period were considered as adverse drug reactions (ADRs) of thiamine.

Statistical analyses were performed using SPSS version 21 software. Kolmogorov–Smirnov test was applied to determine normality of the distribution of quantitative data. Because of the normality of quantitative variables, parametric tests (independent sample *t*-test) were used to compare the quantitative variables in the control and intervention groups. Quantitative variables: data were expressed as mean ± standard deviation (SD). Qualitative variables: data were reported as frequency and percentages. Chi-square or Fisher's exact test were used for comparing the frequency of qualitative variables between control and intervention groups. $P < 0.05$ was considered as statistically significant.

RESULTS

During the study period, 150 patients were assessed for eligibility. Finally, 96 patients were randomly assigned to thiamine and placebo groups [Figure 1]. General characteristics of study participants are shown in Table 1, No significant difference regarding demographic, clinical, and laboratory data was detected between the groups. Baseline diseases, drugs, and surgery data were comparable between the groups [Table 2]. Furthermore, comparing of participants' characteristics during ICU stay found no significant difference between the groups [Table 3]. Gastrointestinal cancer was the most common cause of hospital admission (65.6%) and requiring cardiovascular support was the most common cause of ICU admission (74%).

The incidence rate of delirium over time was significantly lower in the thiamine group than the placebo group on day 1 (8.3% vs. 25%; or: 0.27 [95% confidence interval (CI): 0.08–0.92]; $P = 0.026$) and day 2 (4.2% vs. 20.8%; Odds ratio: 0.16 [95%CI: 0.03–0.81]; $P = 0.014$).

The mean ± SD morphine equivalent doses were not significantly different between the groups [Table 4]. No patient needed haloperidol for control of delirium. Duration of mechanical ventilation was not significantly different between the groups [Table 4]. No adverse effect related to thiamine was detected during the study.
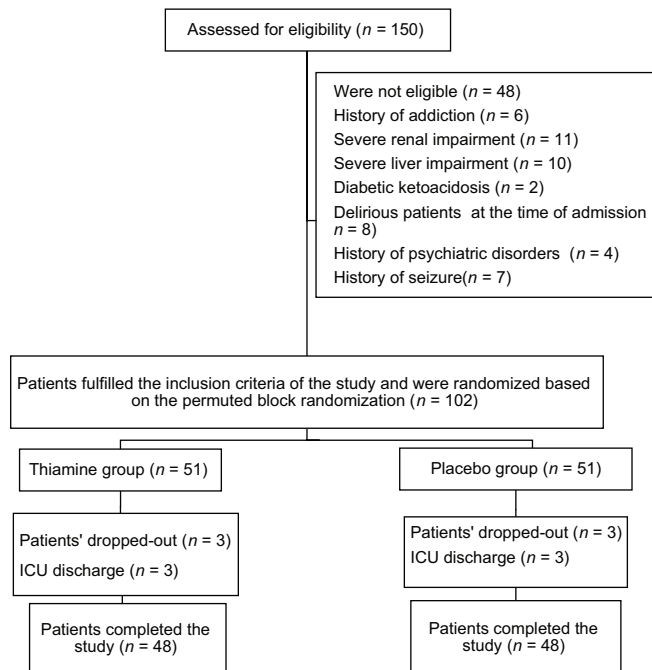
DISCUSSION

In this study, effect of thiamine in the prevention of postoperative delirium in patients undergoing gastrointestinal surgery was evaluated. Included patients had comparable risk factors for incidence of delirium, type of surgery, anesthesia protocol, severity of acute

Table 1: Demographic, clinical, and laboratory data of study participants

Parameters	Thiamine group (*n*=48)	Placebo group (*n*=48)	*P*‡
Age (years), mean±SD*	55±12.8	53±11.4	0.56
Sex, *n* (%)**			
Male	28 (59.57)	29 (60.4)	0.57
Cause of hospital admission, *n* (%)			
Rectal bleeding	1 (2.1)	2 (4.2)	0.64
Crohn's disease	2 (4.2)	0	
Cancer	32 (66.7)	31 (64.6)	
Ulcerative colitis	2 (4.2)	2 (4.2)	
Acute abdominal pain	11 (22.9)	13 (27.1)	
Cause of ICU admission, *n* (%)			
Cardiovascular support	37 (77.1)	34 (70.8)	0.67
Loss of consciousness	2 (4.2)	3 (6.2)	
Respiratory support	8 (16.7)	9 (18.8)	
Hemodynamic support	1 (2.1)	2 (4.2)	
Serum albumin, mean±SD	4.29±5	3.79±0.8	0.50
ESR, mean±SD	26.3±22.5	35.27±28	0.08
CRP, mean±SD	22.25±26	27.22±28.5	0.37

‡*P* value has been examined by Independent sample *t*-test for quantitative variables and Fisher's exact test for nominal variable, *Data have been presented as mean±SD for quantitative variables, **Data have been presented as *n* (%) for nominal variable. ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, SD=Standard deviation, ICU=Intensive care unit

Figure 1: Consort flowchart of the study

Assessed for eligibility (*n* = 150)

Were not eligible (*n* = 48)
History of addiction (*n* = 6)
Severe renal impairment (*n* = 11)
Severe liver impairment (*n* = 10)
Diabetic ketoacidosis (*n* = 2)
Delirious patients at the time of admission *n* = 8)
History of psychiatric disorders (*n* = 4)
History of seizure(*n* = 7)

Patients fulfilled the inclusion criteria of the study and were randomized based on the permuted block randomization (*n* = 102)

Thiamine group (*n* = 51)

Placebo group (*n* = 51)

Patients' dropped-out (*n* = 3)
ICU discharge (*n* = 3)

Patients' dropped-out (*n* = 3)
ICU discharge (*n* = 3)

Patients completed the study (*n* = 48)

Patients completed the study (*n* = 48)

Table 2: Baseline diseases, drugs history, and surgical data of study participants

Parameters	Thiamine group (*n*=48)	Placebo group (*n*=48)	*P*‡
Baseline disease, *n* (%)			
Cardiovascular diseases**	13 (27.1)	8 (16.7)	0.57
Diabetes	5 (10.4)	6 (12.5)	
Gastrointestinal diseases	20 (41.7)	27 (56.2)	
Thyroid diseases	1 (2.1)	1 (2.1)	
Nondisease	9 (18.8)	6 (12.5)	
Past drug history, *n* (%)	41 (85.4)	43 (89.6)	0.37
Statins, *n* (%)	15 (31.1)	9 (18.8)	0.11
Proton pump inhibitors, *n* (%)	13 (27.1)	12 (25)	0.50
H2 blocker, *n* (%)	8 (16.7)	7 (14.6)	0.50
Duration of anesthesia (h), mean±SD*	4.26±1.22	3.87±1.15	0.11
Time of recovery (min), mean±SD	43±12.6	44±12.4	0.52

‡*P* value has been examined by independent sample *t*-test for quantitative variables and Fisher's exact test for nominal variable, *Data have been presented as mean±SD for quantitative variables, **Data have been presented as *n* (%) for nominal variable. SD=Standard deviation

Table 3: Laboratory and clinical data of study participants during intensive care unit stay

Parameters	Thiamine group (*n*=48)	Placebo group (*n*=48)	*P*‡
Liver impairment, *n* (%)**	2 (4.2)	3 (6.2)	0.50
Renal impairment, *n* (%)	1 (2.1)	4 (8.3)	0.18
Hypernatremia, *n* (%)	0	1 (2.1)	0.50
Hypokalemia, *n* (%)	5 (10.4)	3 (6.2)	0.35
Hypomagnesaemia, *n* (%)	4 (8.3)	4 (8.3)	0.64
Anemia, *n* (%)	29 (60.4)	23 (47.9)	0.15
Leukopenia, *n* (%)	3 (6.2)	4 (8.3)	0.50
Thrombocytopenia, *n* (%)	12 (25)	14 (29.2)	0.40
Hypoxemia, *n* (%)	3 (6.2)	4 (8.3)	0.50
Acidosis, *n* (%)	8 (16.7)	12 (25)	0.22
Alkalosis, *n* (%)	1 (2.1)	2 (4.2)	0.50
Hyperglycemia, *n* (%)	3 (6.2)	2 (4.2)	0.50
MAP (mmHg), mean±SD*	91±16.4	95±11.6	0.16
Fever, *n* (%)	13 (27.1)	16 (33.3)	0.32
Antibiotic use during ICU stay, *n* (%)	13 (27.1)	17 (35.4)	0.25
H2 blockers use during ICU stay, *n* (%)	14 (29.2)	15 (31.2)	0.50
PPI use during ICU stay, *n* (%)	34 (70.8)	33 (68.8)	0.50
Anticoagulant use during ICU stay, *n* (%)	47 (97.9)	48 (100)	0.50
Diuretic use during ICU stay, *n* (%)	7 (14.6)	5 (10.4)	0.37
Vasopressor use during ICU stay, *n* (%)	2 (4.2)	2 (4.2)	0.69
Fluid Intake, mean±SD	2585±314	2466±448	0.13
Urine output, mean±S	2305±331	1925±242	0.23
APACHE II score at admission, mean±SD	8.04±2.3	7.14±2.2	0.05
SOFA score day 1, mean±SD	2.43±1.4	2.47±1.4	0.88
SOFA score day 2, mean±SD	1.58±0.98	2.08±1.47	0.05
SOFA score day 3, mean±SD	1.43±1	1.9±1.5	0.07

‡*P* value has been examined by Independent sample *t*-test for quantitative variables and Fisher's exact test for nominal variable, *Data have been presented as mean±SD for quantitative variables, **Data have been presented as *n* (%) for nominal variable. SD=Standard deviation, MAP=Mean arterial pressure, ICU=Intensive care unit, PPI=Proton pump inhibitors, APACHE=Acute Physiology and Chronic Health Evaluation, SOFA=Sequential organ failure assessment

illnesses at the time of ICU admission, organs' function during ICU stay, laboratory, and clinical data.

During the study course, thiamine significantly decreased incidence of delirium on days 1–2 without any adverse reaction compared with placebo.

Delirium is one of the most important postoperative complications in patients undergoing surgery. It is associated with worse outcomes.[24,25] Several aspects of delirium pathophysiology have been described. Neurotransmitters' imbalance (increased dopamine, depletion of acetylcholine, increased glutamate, and serotonin),[19] release of inflammatory mediators (tumor necrosis factor alpha, interlukin-1, and other cytokines) that lead to endothelial damage and microvascular dysfunction in the central nervous system,[26] and cerebral insufficiency secondary to a global failure in oxidative metabolism[19,27] are probable mechanisms.

PDH and α-KGDH require thiamine as a cofactor in the Krebs cycle.[12,14] Furthermore, PDH is essential for the production of acetylcholine. Low level of acetylcholine is associated with cognitive impairment and delirium.[15,28] Interestingly, α-KGDH plays a key role to maintain balance between glutamate and gamma-aminobutyric acid neurotransmitters.[28] This imbalance can lead to excitation and delirium.[16,19]

Thiamine is a required cofactor for mitochondrial synthesis of ATP. Reduced ATP in the brain increased production of toxic metabolites of dopamine which can lead to delirium, hallucination, and delusion.[13,15]

Positive effects of thiamin were investigated in several clinical studies. Thiamine has been shown to have significant analgesic effect in neuropathic pain and nephron protection in acute illnesses.[29,30] In septic shock patients revealed that thiamine group had lower serum creatinine levels and a lower rate of progression to renal replacement therapy than placebo group.[31]

Thiamine deficiency is associated with some neurological problems including cognitive impairment, dementia, and delirium.[15] Thiamine deficiency is common in patients with sepsis and associated with an increased risk of death.[32] Experimental studies showed that thiamine and riboflavin enhanced the anti-inflammatory effect of dexamethasone.[33] Thiamine also increased oxygen uptake in critically ill patients requiring mechanical ventilation with preserved cardiac index.[34] Thiamine improved cardiac function in symptomatic patients with chronic heart failure.[14] In González-Ortiz *et al*.'s study, thiamine administration for 1 month decreased glucose and leptin concentration in drug-naıve patients with T2DM.[35]

Preventing postoperative delirium is effective approach to minimize adverse outcomes in patients.[36,37] Among medical interventions, antipsychotic medications mostly were examined for prevention and treatment of delirium. Prophylaxis with low dose of haloperidol resulted in a lower incidence of delirium in critically ill patients after noncardiac surgery.[20] Furthermore, in a trial that compared prophylactic effect of olanzapine versus placebo, there was a significant decrease in the incidence of postoperative delirium in olanzapine group.[38]

Table 4: Outcomes of the study participants				
Outcomes	Thiamine group (*n*=48)	Placebo group (*n*=48)	Mean difference (95%CI)	*P*‡
Delirium on day 1 (morning), *n* (%)**	4 (8.3)	12 (25)	0.27 (0.08-0.92)	0.026
Delirium on day 1 (night), *n* (%)	4 (8.3)	12 (25)	0.27 (0.08-0.92)	0.026
Delirium on day 2 (morning), *n* (%)	2 (4.2)	10 (20.8)	0.16 (0.03-0.81)	0.014
Delirium on day 2 (night), *n* (%)	2 (4.2)	9 (18.8)	0.18 (0.04-0.92)	0.025
Delirium on day 3 (morning), *n* (%)	3 (6.2)	8 (16.7)	0.33 (0.08-1.34)	0.99
Delirium on day 3 (night), *n* (%)	3 (6.2)	7 (14.6)	0.39 (0.09-1.61)	0.15
Analgesic equivalent morphine dose during ICU stay on day 1, mean±SD*	9±2.6	8.7±2.4	0.29 (−0.74-1.32)	0.26
Analgesic equivalent morphine dose during ICU stay on day 2, mean±SD	7.18±2.4	7.7±2.4	−0.54 (−1.53-0.44)	0.71
Analgesic equivalent morphine dose during ICU stay on day 3 , mean±SD	6.5±2.3	6.6±2.3	−0.083 (−1.03-0.86)	0.50
Days of mechanical ventilation (day), mean±SD	1.8±1.9 (*n*=5)	2.14±0.89 (*n*=7)	−0.34 (−0.89-0.68)	0.47

‡*P* value has been examined by Independent sample *t*-test for quantitative variables and Fisher's exact test for. nominal variable, *Data have been presented as mean±SD for quantitative variables, **Data have been presented as *n* (%) for nominal variable. SD=Standard deviation, CI=Confidence interval, ICU=Intensive care unit

Incidence of delirium significantly declined following administration of ramelteon for elderly patients in ICU.[39] However, oral acetyl cholinesterase inhibitors (donepezil 5 mg/day and rivastigmine 4.5 mg/day) failed to prevent postoperative delirium.[7]

Although several interventions were examined, unfortunately, no safe medication has been found for prevention of delirium in postoperative patients yet. Antipsychotic drugs are associated with various serious ADRs such as metabolic disorders, cardiovascular events, and neuroleptic malignant syndrome.[9-11] Other medications are also accompanied by ADRs like bradycardia for dexmedetomidine and donepezil.[6,7] However, no ADR related to thiamine was detected during this study. Protective effect of thiamine against postoperative delirium suggests a possible role of neuroinflammation in delirium.

The small sample size and short duration of intervention were limitations of this study. Furthermore, it was not feasible to assess whole-blood thiamine concentration. Well-designed controlled randomized trial considering different doses of thiamine, administration of thiamine before the operation in high-risk patients, and concomitant administration of thiamine with other drugs such as quetiapine or dexmedetomidine are recommended for future studies.

The results suggest that administration of IV thiamine in patients after gastrointestinal surgery admitted in ICU was associated with a lower incidence of delirium postoperatively. Thiamine seems to be a safe option for the prevention of postoperative delirium.

AUTHORS' CONTRIBUTION

Rohollah Moslemi: Data gathering and primary drafting of the manuscript. Hossein Khalili: Designing of the study and editing the manuscript. Mostafa Mohammadi: Clinical evaluation of the patients. Zeinab Mehrabi, Niayesh Mohebbi: contributed in manuscript preparation and editing.

Conflicts of interest

There are no conflicts of interest.

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