

## The neurotransmitters imbalance in participants receive cytotoxic agents

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SUMMARY

Neurotransmitters are endogenous chemical compounds that have the ability for neurotransmission and play a major role in shaping everyday life and functions. Cytotoxic drugs are a type of cancer and other diseases like rheumatoid arthritis, SLE, and different autoimmune syndromes treatment that utilize one or more chemotherapeutic agents as part of a regimen. The study aims are to calculate levels of neurotransmitters in patients receiving cytotoxic drugs and determined the effect of these agents on NTs concentration before and after. A prospective comparison study carried out before and after receives cytotoxic treatment for a period of three months from June 2020 to September 2020. Assessments of the studied samples will be conducted as a baseline before and after receiving drugs. A total of 50 participants were involved in the study. The blood samples were collected about 5 ml and diluted in the concentrated washing solution. The neurotransmitters evaluated are Adrenaline, Acetylcholine, Dopamine, Histamine, Glutamate, GABA, Serotonin, and Somatostatin. The mean age of the sample of the study was  $49.28 \pm 12.44$ . Patients with comorbidity conditions were 60%. The mean acetylcholine concentration pre and post receiving cytotoxic drugs was relatively not altering. Cytotoxic agents affected the mean epinephrine concentration, which was directly dropping to half. There was a decline of concentration of somatostatin post treatment compared with pre (from  $33.83 \pm 9.78$  ng/L to  $8.4 \pm 2.66$  ng/L), with a significant association (t-test=2.3, p=0.028). The mean concentration of dopamine pre was relatively unchanged from post-treatment. There was no differences association between pre and post mean level of histamine in this study. In this study, we found a high level of glutamine in the pre-phase ( $2025.4 \pm 753.7$   $\mu$ mol/L), but it converted to normal level post treatment, with statistically significant differences (t-test=9.051, p<0.000). GABA concentration, the pre was above the normal range ( $1.31 \pm 0.18$   $\mu$ mol/l), while the post was within normal, this dropping curve was statistically significant differences (t-test=9.442, p<0.000). There was a slight decrease in serotonin level among pre to post (from  $366.6 \pm 237.72$  ng/mL to  $298.77 \pm 231.8$  ng/mL), but these changes not significant. In conclusion, the NTs concentration may be altered by the administration of cytotoxic drugs in chronic diseases in a different pattern either decrease or return to normal.

**Key words:** neurotransmitters, cytotoxic agents, CNS tumours, adrenaline, acetylcholine, dopamine, histamine, glutamate, GABA, serotonin, somatostatin

## INTRODUCTION

Neurotransmitters are endogenous chemical compounds that have the ability for neurotransmission by carrying messages among neurons via influence on the postsynaptic membranes, changing the structures of the synapse, and communicate by sending reverse-direction messages that affect the release or reuptake of transmitters [1]. It transmits signals across a chemical synapse, such as a neuromuscular junction, from one neuron to another neuron, muscle cell, or gland cell, and is released from synaptic vesicles in synapses into the synaptic cleft, where they are received by receptors. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which are readily available from the diet. Neurotransmitters play a major role in shaping everyday life and functions [1].

Cytotoxic drugs are a type of cancer and other diseases like rheumatoid arthritis, SLE, and different autoimmune syndromes treatment that utilize one or more chemotherapeutic agents as part of a regimen [2]. The traditional chemotherapeutic agents are almost always cytotoxic, are interfering with cell division (mitosis), besides that the chemotherapy destroys cells whether cancerous or healthy, which may then lead to cell death [2]. Chemotherapy side effects are traced to destroy normal cells that divide rapidly and thus include cells in the bone marrow, digestive tract, and hair follicles [2,3].

There are several modalities in the administration of chemotherapeutic drugs [2,4-7], including: Induction, combined, consolidation, intensification, combination, neoadjuvant, adjuvant and salvage or palliative chemotherapy.

In this research, we try to compare NTs concentrations at pre and post-treatment with cytotoxic drugs using different morbid and chronic diseases like CNS tumours, RA, SLE, and others.

## METHODS

### Study design and setting

A prospective comparison study carried out before and after receives cytotoxic treatment for a period of three months from June 2020 to September 2020. Assessments of the studied samples will be conducted as a baseline before and after receiving drugs. A total of 50 participants were involved in the study, who accepted patient inform consent.

### Inclusion criteria

- Patients before undergo the first cycle of cytotoxic.
- Those who have to agree to involvement in the study.

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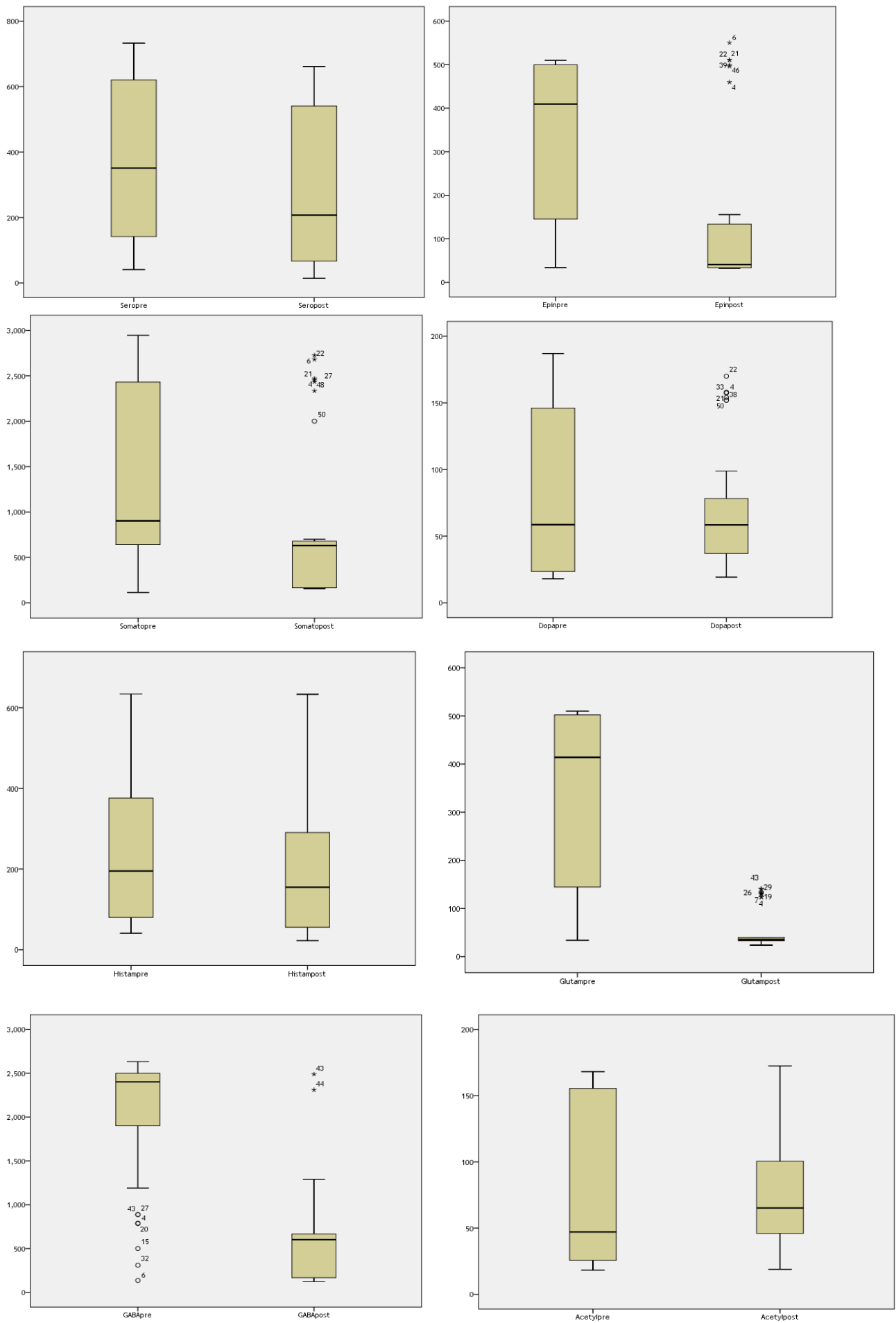


Fig. 1. Box plot of neurotransmitters concentration before and after cytotoxic

### Exclusion criteria

- Patients who changing drugs protocols.
- Those refused study entrance from the beginning.
- Those whom referral from another centre.
- Patients receiving chemotherapy previously.
- Uncomfortable.

### Data measurement

The blood samples were collected about 5 ml put in a refrigerator before and including the day of the sample collection (Figure 1).

at 4°C. Taken test when it balances to room temperature and diluted the concentrated washing solution with double distilled water (1:25). Each neurotransmitter kit has its directions and steps of preparation procedure as mention in the special leaflets.

### Neurotransmitters

Adrenaline (epinephrine), Acetylcholine, Dopamine, Histamine, Glutamate, GABA, Serotonin, and Somatostatin. Foods or liquids such as pineapple, eggplant, avocados, bananas, currants, kiwis, melon, mirabelles, plums, peaches chocolate, gooseberries, tomatoes, or walnuts, should be avoided 2 days

Tab. 1. All study variables (n=50)		Variables	No. (%)	Mean ± SD
<b>Gender</b>		Male	25 (50)	
		Female	25 (50)	
		Total	50	
<b>Age (years)</b>		21-30	3 (6)	
		31-40	6 (12)	
		41-50	20 (40)	
		51-60	10 (20)	
		61-70	11 (22)	
		Total	50	49.28 ± 12.44
<b>Address</b>		Urban	37 (74)	
		Rural	13 (26)	
		Total	50	
<b>Occupation</b>		Employer	20 (40)	
		Housewife	15 (30)	
		Non- employer	10 (20)	
		Student	5 (10)	
<b>Comorbidity</b>		Total	50	
		Present	30 (60)	
		Not present	20 (40)	
<b>BSA (m<sup>2</sup>)</b>		<1.7	25 (50)	
		≥ 1.7	25 (50)	
		Total	50	1.66 ± 0.13
<b>BMI (m<sup>2</sup>/Kg)</b>		Normal (18.6-24.9)	15 (30)	
		Overweight (25-29.9)	30 (60)	
		Moderate obesity (30-34.9)	3 (6)	
		Severe obesity (35-39.9)	2 (4)	
		Total	50	35.77 ± 3.63
<b>Diseases</b>		Cancers (CNS tumors)	12 (24)	
		Rheumatoid arthritis	20 (40)	
		SLE	8 (16)	
		Autoimmune syndromes	6 (12)	
		Others	4 (8)	
		Total	50	
<b>Cytotoxic</b>		R-CHOP	38 (76)	
		Temodalizamide	8 (16)	
		Vincristine	4 (8)	
		Total	50	

**Tab. 2.** Comparison between NTs concentration pre-and post-cytotoxic administration

NTs (Normal range)	Paired Differences				t	df	p-value (2-tailed)
	Pre	Post	95% Confidence Interval				
			Lower	Upper			
Acetyl choline (8-18 U/mL)	7.68 ± 5.85	7.86 ± 4.75	-2.735	8.369	-0.145	37	0.885
Epinephrine (<273 pmol/L)	301.1 ± 193.68	141 ± 168.6	89.66	230.6	4.6	36	0
Somatostatin (<25 ng/L)	33.83 ± 9.78	8.4 ± 2.66	6.68	10.92	2.3	34	0.028
Dopamine (<87pg/mL)	82.1 ± 59.5	71.4 ± 44.4	-16.78	38.06	0.789	33	0.436
Histamine (≤10 nm/mL)	25.26 ± 19.72	20.23 ± 18.11	-9.33	10.98	1.705	40	0.096
Glutamine (550-750 μmol/L)	2025.4 ± 753.7	563.8 ± 531.2	1134.39	1788.79	9.051	37	0
GABA (0.2-0.8 μmol/l)	1.31 ± 0.18	0.53 ± 0.39	0.2	1.31	9.442	40	0
Serotonin(50-200 ng/mL)	366.6 ± 237.72	298.77 ± 231.8	-19.97	155.65	1.565	37	0.126

**Statistical**

We used mean and SD to represent the data while describing variables presented using their frequencies and parentage. One way paired T-test for variables was used. SPSS version 24 was used for data entry and analysis. P-value was considered significant if <0.05.

**RESULT**

**Patient’s demographic variables**

25(50%) of patients were females and 25(50%) were males. The mean age of the sample of the study was 49.28 ± 12.44 years with a median of 50 years. Most patients were from urban areas 37(74%), and the rest from rural 13(26%). Most female patients were housewives. Patients with comorbidity conditions were 60%.

Regarding Body Surface Area (BSA), we recorded 50% of patients with BSA equal or less than 1.7 m<sup>2</sup> for each. The mean Body Mass Index (BMI) of patients was 35.77 ± 3.63 m2/Kg. Most patients figured to overweight 60%.

The majority of patients suffered from RA 40%. The most regimens of drugs used were RCHOP (cyclophosphamide and rituximab) in 76% of patients (Table 1).

Our findings showed that the mean acetylcholine concentration pre and post receiving cytotoxic drugs was relatively not altering (from 7.68 ± 5.85 U/mL to 7.86 ± 4.75 U/mL), with no significant differences (t-test=0.145, p=0.885). Cytotoxic agents affected the mean epinephrine concentration, which was directly dropping to the half (from 301.1 ± 193.68 pmol/L to 141 ± 168.6 pmol/L), with strong statistical significant differences (t-test=4.6, p=0.000).

There was a massive decline of concentration of somatostatin post treatment compared with pre (from 33.83 ± 9.78 ng/L to 8.4 ± 2.66 ng/L), with a significant association (t-test=2.3, p=0.028).

The mean concentration of dopamine pre was 82.1 ± 59.5 pg/mL, whereas it was 71.4 ± 44.4 pg/mL post-treatment. These findings were not significant (t-test=0.789, p=0.436).

There was no differences association between pre (25.26 ±

19.72 nm/mL) and post (20.23 ± 18.11 nm/mL) mean level of histamine in this study (t-test=1.705, p=0.096).

In this study, we found a high level of glutamine in the samples in pre-phase (2025.4 ± 753.7 μmol/L), but it converted to normal level post-treatment (563.8 ± 531.2 μmol/L), with statistically significant differences (t-test=9.051, p<0.000).

Regarding GABA concentration, the pre was above the normal range (1.31 ± 0.18 μmol/l), while the post was within normal (0.53 ± 0.39 μmol/l). The dropping curve was statistically significant differences (t-test=9.442, p<0.000).

There was a slight decrease in serotonin levels among pre to post (from 366.6 ± 237.72 ng/mL to 298.77 ± 231.8 ng/mL), but these changes not significant (t-test=1.565, p=0.126) (Table 2).

**DISCUSSION**

Nausea and vomiting are common side effects of chemotherapy and molecular-targeted therapy. With the advent of newer agents used to treat Chemotherapy-Induced Nausea and Vomiting (CINV), the incidence has greatly decreased; however, this

Continues to be a significant cause of concern to patients. The incidence of acute CINV (within 24 hours of drug administration) is estimated to be 37% to 59% and delayed CINV (>24 hours after administration) occurs in 47% to 75% of patients treated with chemotherapy [8,9]. Although emesis appears to be better controlled with the newer antiemetic agents, nausea is still a problem and can adversely affect the patient’s quality of life [9-11]. CINV can cause a decrease in quality of life [10], disruption in treatment schedules, decrease in compliance, medical complications such as dehydration, poor nutrition, electrolyte imbalance, frequently resulting in hospitalization, and elevation in the costs of health care and loss of workdays [12].

There has been a lot of work done in the past couple of decades toward elucidating the pathophysiology of CINV, which is complex and involves several pathways. The concept of a single “vomiting centre” in the brain proposed by Wang and Morison in 1950 is now replaced by a complex set of neurons called the “central pattern generator,” believed to coordinate the series of events that lead to emesis, as proposed by Koga and Fukuga in 1992 [6].

It is now believed that the principal actors are the neurotransmitter receptors for serotonin 5-hydroxy tryptamine 3 (5HT<sub>3</sub>), dopamine, substance P, and cholecystokinin, which are located in the entero-chromaffin cells in the small intestinal epithelium and are the terminal ends of vagal afferents. Antineoplastic agents stimulate these vagal afferents either by direct toxicity or by breaking of the mucosal barrier and causing the release of neurotransmitters from the entero-chromaffin cells, which then bind to the receptors; the stimulus is carried to the dorsal brain stem (NTS and area postrema) and activates the central pattern generator [13].

Area postrema contains the chemotherapy trigger zone and may have different mechanisms of activation, which are incompletely understood. The amygdala is another less-understood area of the brain that is associated with CINV. 5HT receptors are found in all three key areas: the vagal afferent chain, NTS, and area postrema. 5HT<sub>3</sub> is the most important of all of the receptors in mediating CINV. It has been shown that the abdominal vagal afferents are the principal mediators of CINV with 5HT<sub>3</sub> agonists [14]. Although dopamine, 5HT<sub>3</sub>, and substance P (a neurokinin) all exert pro-emetic effects, endocannabinoids have antagonistic action [14, 15].

The size of neurotransmitters is about the size of one amino acid; but, some neurotransmitters may be larger than the size of proteins or peptides. The short-term exposure of the receptor to a neurotransmitter is typically sufficient for causing a postsynaptic response by way of synaptic transmission, this leads to a threshold action potential, and then a neurotransmitter is released at the presynaptic terminal. The released neurotransmitter may then move across the synapse to be detected by and bind with receptors in the postsynaptic neuron. The binding of neurotransmitters may influence the postsynaptic neuron in either an inhibitory or excitatory pathway [16,17].

The different functions of acetylcholine, glutamate, GABA, glycine, dopamine, norepinephrine, and serotonin play important and different roles in body physiology. Glutamate is the excitatory neurotransmitter used in the brain and acts as the primary mediator of nervous system plasticity by modifying synapses, which researchers suspect are the memory-storage elements of the brain. Whereas, Gamma-Aminobutyric Acid (GABA) and glycine, serve as the main inhibitory neurotransmitters [16, 17].

Dopamine, plays an essential role in several brain functions, like learning, motor control, reward, emotion, and executive functions, besides implicated in psychiatric and neurological disorders [18]. Serotonin is modulating multiple neuropsychological processes and neural activity, which has implications that affect gastrointestinal processes like bowel motility, bladder control, and cardiovascular function [19].

Epinephrine is a monoamine that is synthesized in the central

nervous system, and when the release of norepinephrine in the brain exert effects on a variety of processes, involving stress, sleep, attention, focus, and inflammation. In addition, play important roles in modulating the responses of the autonomic nervous system [20].

Specifically, calcium-evoked exocytosis of the presynaptic vesicles is enabling the release of neurotransmitters into the synapse. The active zones on the presynaptic plasma membranes, bond the neurotransmitter-containing vesicles to the plasma membrane. Once an action potential triggers calcium influx into the presynaptic cleft, the zones undergo fusion with the vesicles, allowing neurotransmitter releasing [21]. Many proteins are involved in the process of fusion between neurotransmitter-containing vesicles and the active zone. The main one is the soluble N-ethyl maleimide Sensitive Factor Attachment Protein Receptors (SNAREs) syntaxin-1, SNAP-25, and others like synaptobrevin-2, which together form a SNARE complex, act as a key component in membrane fusion [21, 22].

Glutamate is including in many neurodegenerative published studies. Glutamate has been excitotoxicity undoubtedly which plays a role in the pathogenesis of Alzheimer's disease and Parkinson's syndrome, and it accelerates the progression of these diseases [23]. Gamma-Aminobutyric Acid (GABA) is a targeted factor in the treatment of anxiety disorder, insomnia, epilepsy [21].

Dopamine plays an essential role in many physiological processes, also it has a role in the pathology of psychiatric and neurodegenerative diseases. Disturbances in the neurotransmission of dopamine are implicated in schizophrenia, psychosis, depression, and attention deficit hyperactivity disorder. There is a degeneration of dopaminergic neurons in the substantia nigra pars compacta is involved in the pathogenesis of these diseases [24].

Serotonin control several neuropsychiatric processes have been implicated in the pathogenesis of depression, when patients exposure to endogenous depression, they have low plasma levels of tryptophan, which is a precursor of serotonin [19]. Norepinephrine is involved in the pathogenesis of neuropsychiatric disorders such as anxiety disorders, mood disorders, attention-deficit hyperactivity disorder, Alzheimer's disease, and posttraumatic stress disorder [25].

## CONCLUSION

Most of NTs dropping level occurs after receiving cytotoxic drugs, but this stay within the normal range of concentration in the body.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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