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Tryptophan Supplementation and Postoperative Delirium – A Randomized Controlled Trial

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Abstract

Background/Objectives—Tryptophan deficiency has been associated with increased incidence of postoperative delirium. Therefore, we hypothesized that the post-operative administration of tryptophan would be beneficial for elderly surgical patients who are at higher risk of developing post-operative delirium.

Design—Randomized, double-blind, placebo controlled trial.

Setting: Participants—A total of 325 individuals aged 60 years and older undergoing major elective operations requiring a postoperative intensive care unit admission.

Intervention—L-tryptophan, 1 gram orally, three times daily or placebo was started following the operation and continued for up to three days postoperatively.

Measurements—Delirium and its motor subtypes were measured using the Confusion Assessment Method-ICU and the Richmond Agitation and Sedation Scale. The primary outcome for between groups comparison was the incidence of excitatory (mixed and hyperactive) postoperative delirium. The secondary outcomes for comparison were the incidence and duration of overall postoperative delirium.

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Author Contributions:

Concept and design – Robinson, Moss

Acquisition of subjects and/or data – Robinson, Dunn, Adams, Hawkins, Raeburn

Analysis and interpretation of data – Robinson, Dunn, Tran, Moss

Preparation of manuscript – Robinson, Dunn, Adams, Hawkins, Tran, Raeburn, Moss

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Results—The overall incidence of postoperative delirium was 39% (116) (95% confidence interval 34% to 44%). The percentages of patients with excitatory delirium in the tryptophan and placebo groups were 17% and 9% ($p=0.176$), and the duration of excitatory delirium was 3.3 ± 1.7 and 3.1 ± 1.9 days ($p=0.741$). The percentage of patients with overall delirium in the tryptophan and placebo groups was 40% and 37% ($p=0.597$), and the duration of overall delirium was 2.9 ± 1.8 and 2.4 ± 1.6 days ($p=0.167$).

Conclusion—Postoperative tryptophan supplementation in older adults undergoing major elective operations requiring postoperative intensive care unit admission demonstrated no efficacy in reducing the incidence of postoperative excitatory delirium or overall delirium, and the duration of excitatory or overall delirium.

Keywords

delirium; organic brain syndrome; geriatric surgery; acute confusion

INTRODUCTION

Post-operative delirium is a common and deleterious complication in older patients.¹ The incidence of delirium following an operation has been estimated to be between 15–53%;² leading some to recognize delirium as the most common postoperative complication in older adults.³ Delirium is a critically relevant complication because of delirium's close relationship to poor outcomes, including increased complications, longer length of stay, higher need for discharge to an institutional care facility, poorer functional recovery, increased mortality, impaired cognition and higher postoperative costs.^{4–7} Developing strategies to prevent or treat postoperative delirium is vital for optimizing the surgical care of our aging population.

Neurotransmitter alterations within the central nervous system almost certainly play an important primary role in the pathogenesis of delirium.⁸ Serum amino acids, and in particular tryptophan, have been highlighted as a promising area to investigate the etiology and potential treatment of delirium⁹ because tryptophan is an amino acid precursor to the delirium-relevant neurotransmitters serotonin and melatonin.¹⁰ The final neurotransmitter in the tryptophan metabolism pathway is melatonin which is a sedating neurotransmitter and causes drowsiness.¹¹ Tryptophan homeostasis is well described to be disrupted in the post-operative setting. Our work,¹⁴ in addition to that of others,^{15,16} found lower post-operative levels of tryptophan in patients who develop delirium.

Postoperative delirium presents in a spectrum of psychomotor behavior described clinically as the motor subtypes of delirium.^{17,18} The excitatory (hyperactive or mixed) subtypes of delirium are particularly relevant to hospitalized surgical patients because they have been related to inpatient falls,¹⁹ inadvertent surgical line/tube removal,¹⁷ and are treated with antipsychotic medications which are related to negative outcomes.²⁰ Tryptophan supplementation which leads to increased levels of the sedating neurotransmitter melatonin has the potential to reduce the excitatory motor subtypes of postoperative delirium. Because our preliminary data found lower levels of tryptophan in delirious patient on postoperative

day two,¹⁴ we decided supplementation of tryptophan postoperatively may be most beneficial.

We hypothesized that oral tryptophan supplementation, post-operatively, would reduce the excitatory (both hyperactive and mixed) delirium motor subtype. The specific aims of this study were to compare the effect of tryptophan supplementation to placebo on the occurrence of postoperative delirium including: (1) incidence of postoperative excitatory (mixed and hyperactive) delirium; (2) incidence of overall postoperative delirium; (3) duration of postoperative excitatory (mixed and hyperactive) delirium; and (4) duration of overall postoperative delirium.

METHODS

This double blinded, randomized, placebo controlled trial was performed at the Denver Veterans Affairs Medical Center. The Colorado Multiple Institutional Review Board (COMIRB 08-0543) approved this study. Food and drug administration investigation permission to proceed was IND-102,275. Clinical trial registration (www.clinicaltrials.gov) was NCT00865202. There were no changes in study design after the trial commenced.

Participants

Inclusion criteria were patients 60 years and older, undergoing an elective operation with a planned postoperative intensive care unit admission on the general, vascular, urologic and thoracic surgery services. Exclusion criteria were emergent operations (defined as an operation within 12 hours of admission), urgent operations (defined as an operation between 12 and 72 hours following admission), medications that increase serotonin levels or lower seizure threshold (including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, see Appendix 1 for complete list), blind patients (cannot be assessed by delirium assessment tool), pre-existing eosinophilia (eosinophils>6%), alcohol abuse defined as an Alcohol Use Disorders Identification Test (AUDIT) score of 8 for males and 5 for females,²¹ significant liver disease (Childs-Pugh class B or C),²² and renal impairment defined as a creatinine clearance <40.

Intervention

Subjects were randomized to receive either L-tryptophan (Amino Acids, Inc., California) 1 gram enterally three times per day or similar appearing placebo (parallel design, allocation 1:1). Study drug administration was continued for a total of nine doses or until the patient was discharged from the surgical intensive care unit. The initial dose of study drug or placebo was administered on the evening of the operation. Randomization was performed by the research pharmacy using a computer-generated sequence, block randomized in groups of 40. The research pharmacy assigned participants to interventions. The research team recruited participants.

Patients were initially approached in preoperative clinic or pre-anesthesia clinic. Study drug was labeled in sequentially numbered containers to conceal allocation assignment. The research team and the participants were blinded to group assignment. Only the research pharmacist knew the group assignment. Treating physicians and healthcare professionals

were blinded to treatment assignment. Unblinding of study groups was made directly from the research pharmacist to the study biostatistician.

Outcomes

The primary outcome measure was the incidence of the motor subtype of excitatory (mixed and hyperactive) delirium. The secondary outcomes were the duration of the motor subtype of excitatory (mixed and hyperactive) delirium, and the incidence and duration of overall delirium. Outcomes were examined by an intention to treat analysis. Postoperative delirium was defined as previously described by our group.^{4,17} Briefly, the Confusion Assessment Method-ICU (CAM-ICU)²³ was administered daily by a member of the trained research team. A total of five researchers performed the CAM-ICU during the four year study period. Inter-observer reliability for the research team administering the CAM-ICU was established prior to starting the study with a minimum concordance rate of 98% and a kappa statistic of 0.96 (95% confidence interval, 0.91 to 1.00). Patients were assessed for delirium using the CAM-ICU until discharge from the intensive care unit. In addition to the CAM-ICU, a validated chart review method was performed at the same time as the CAM-ICU administration which searched for keywords in the chart for an acute confusional state.²⁴ Delirium was designated as present if either the CAM-ICU or validated chart review were positive. Duration of delirium defined by total number of days that delirium was assessed as present in a subject (with 7A to 7A being defined as one day). Even with the daily delirium assessment and the validated chart review, the fact that delirium fluctuates over time means that some delirium events could have been missed. The delirium motor subtype was defined using the daily RASS scores as previously described.²⁵ Hyperactive delirium was present in subjects with all positive daily RASS scores. Hypoactive delirium was present in subjects with all negative daily RASS scores. Mixed type delirium was present when daily RASS scores included both positive and negative values.

Baseline Data Recorded

Pre-, intra- and post-operative variables were recorded. Baseline preoperative assessment included cognition assessed by the Mini-Cog,²⁶ function as independent or dependent in one or more activity of daily living, mobility with the timed up-and-go,²⁷ having fallen in the past six-months,²⁸ depressed mood measured by the two question depression screen,²⁹ co-morbidity burden by the Charlson Index,³⁰ American Society of Anesthesiologists (ASA) score³¹ and co-morbidities as defined by definitions used by the National Surgical Quality Improvement Program as previously described.³² The baseline preoperative variables were collected and recorded on the morning of the operation. Routine intra-operative variables were recorded. Post-operative variables included complications in the systems of cardiac, pulmonary, renal, neurologic, infectious, sepsis, thrombotic, reoperation and death all defined by NSQIP definitions as previously described.³² Other potential confounding variables for the occurrence of delirium recorded included percent of patients on a ventilator for one or more days, narcotic administration (reported as equivalents of intravenous morphine averaged per day for the first three postoperative days), benzodiazepine administration (reported the percent of subjects who received a benzodiazepine in the first three postoperative days), the percent of patients who received haloperidol during the first three postoperative days, the average hours of sleep over the first three postoperative days,

and the average pain score on a scale of 1 to 10 during the first three postoperative days. Serum tryptophan, serotonin and melatonin levels were determined on the morning of the operation and on the morning of postoperative day number two.

Safety and Adverse Event Monitoring

As required by the FDA, all participants while on study drug had eosinophil count recorded, and underwent daily evaluations for eosinophilia myalgia and serotonin syndrome. A data monitoring committee completed semi-annual reviews of the study. Adverse events attributed to the study drug were recorded.

Sample Size

Sample size calculation was performed using prior information, based on a 19% (18/95) incidence of excitatory (mixed or hyperactive) delirium point estimate from our previous work in a similar population.¹⁷ We assumed a 60% reduction in excitatory delirium in the tryptophan group. For 80% power, using a two-sided chi-square test of proportions, with $\alpha=0.05$, and assuming a 15% dropout rate, 325 total subjects (138 evaluable subjects in each group) were needed to detect a difference. There was no interim analysis performed.

Statistical analysis

Prior to any statistical analysis, descriptive statistics were generated to evaluate the distribution characteristics of all variables, including examination for outliers. Demographic characteristics of patients were examined to assure similarity between groups.

Nominal variables were expressed as proportions and percentages; continuous variables were expressed as means and standard deviations. Between groups differences for proportions were tested using chi-square analysis; between groups differences for continuous variables were tested using t-tests. All statistical tests were 2-tailed, and conducted at the 5% significance level. All data management and statistical analysis were performed using SPSS v21.0

RESULTS

Enrollment

Between December 17, 2008 and December 14, 2012, 731 consecutive patients were screened and 325 patients enrolled. (See Figure 1) Twenty-four patients were withdrawn. The reasons for withdrawal are described in Figure 1. Analysis included 301 patients (152 in L-tryptophan group and 149 in the placebo group). All randomized patients were observed throughout their intensive care unit stay. The trial ended when the planned number of participants was enrolled.

Baseline Characteristics and Surgical Outcomes

Preoperative baseline characteristics were similar in the two groups. (see Table 1) Intra-operative characteristics were not different between the two groups except for vascular operations, which were more common in the L-tryptophan group (27 of 41) in comparison to the placebo group (14 of 41). (See Table 1) Postoperative outcomes including

complications, length of stay and mortality were similar in the two groups. (see Table 2) Variables which represent potential confounders for the occurrence of delirium between the two groups were similar, including: percent of patients receiving one or more doses of a benzodiazepine or haloperidol, pain score, number of hours of sleep and narcotic use (equivalents of morphine) averaged in the first three days, and percent of patients who required one or more days of mechanical ventilation. (See Table 2)

Delirium Outcomes

Delirium overall occurred in 39% and excitatory delirium occurred in 13% of the total study population. The incidence of postoperative excitatory (mixed and hyperactive) delirium (primary outcome variable) was not different between the tryptophan supplementation and placebo groups. (see Table 3) The incidence of overall postoperative delirium; duration of postoperative excitatory (mixed and hyperactive) delirium, duration of overall postoperative delirium, time to presentation of excitatory delirium and the time to presentation of overall delirium was not different between the tryptophan supplementation and placebo groups. (see Table 3) Of patient defined as delirium positive, 87% (261) had a positive CAM-ICU assessment and 13% (38) were delirium positive only by the validated chart review. The number of patients diagnosed with delirium only by validated chart review was similar in the tryptophan (10% (15)) and placebo (15% (23)) groups ($p=0.167$).

Tryptophan Biomarkers

Baseline preoperative levels of tryptophan, serotonin and melatonin were not different between the tryptophan supplementation and placebo groups. Postoperatively, the tryptophan supplementation group had higher levels of serum tryptophan (65 ± 26 umol/L) in comparison to the placebo group (41 ± 15 umol/L; $p<0.001$). Postoperatively, serum serotonin (76 ± 75 versus 83 ± 54 ng/mL; $p=0.483$) and melatonin (78 ± 145 versus 52 ± 63 g/mL; $p=0.126$) were not different in the tryptophan supplementation and placebo groups.

Post-hoc comparison of postoperative tryptophan levels was performed with the goal of either confirming or refuting the preoperative pilot data (the fact that tryptophan levels were lower in patients who developed delirium compared to those who did not develop delirium on post-operative day number 2)¹⁴ that led to this study's hypothesis. In the tryptophan supplementation group, tryptophan levels were lower in the delirious patients (56 ± 18 umol/L) compared to the non-delirious patients (73 ± 30 umol/L; $p<0.001$). In the placebo group, tryptophan levels were similar in delirious patients (38 ± 20 umol/L) compared to non-delirious patients (43 ± 16 umol/L; $p=0.099$).

Study Drug Administration

Missed study drug doses occurred in 6% of the total study group. Similar numbers of missed doses occurred in the tryptophan supplementation and placebo groups. (see Table 4) Side effects attributed to the study drug occurred in 12% of the total study group. Side effects attributed to the study drug occurred similarly in the tryptophan supplementation and placebo groups.

DISCUSSION

In this double blinded placebo controlled trial, postoperative tryptophan supplementation in older adults undergoing major elective operations requiring postoperative intensive care unit admission demonstrated no efficacy in reducing the incidence of postoperative excitatory delirium. Additionally, postoperative tryptophan supplementation in comparison to placebo did not alter duration or time of initial presentation of both excitatory and overall delirium. Variables which represent potential confounders to the development of postoperative delirium were similar in the two groups (including preoperative cognition, chronic disease burden, functional dependence, intraoperative time, blood loss, blood transfusions, postoperative narcotic usage, days on ventilator, pain scores and sleep). Serum biomarker analysis found higher serum tryptophan levels in patients in the tryptophan supplementation group in comparison to the placebo group; a finding that suggests the lack of efficacy of tryptophan on postoperative delirium in these study patients was not due to failure of tryptophan absorption. Missed study drug doses and side effects attributed to the study drug were similar in the two study drug groups; a finding that suggests the lack of efficacy of tryptophan on postoperative delirium in these study patients was not due to inadequate drug delivery.

The effect of tryptophan, and its downstream effect on serotonin and melatonin are important.^{15,339} Two previously published randomized clinical trials have found that melatonin supplementation for hospitalized older adults reduces the occurrence of postoperative delirium.^{34,35} Sultan and colleagues³⁴ studied patients aged 65 years and older without delirium scheduled for hip arthroplasty. Patients received melatonin 5mg or placebo both the evening before and 90 minutes before the operation. The melatonin group had reduced postoperative delirium (9%) in comparison to placebo (34%; $p=0.003$). Al-Aama and colleagues³⁵ studied hospitalized patients 65 years and older admitted to a medical unit. Patients received melatonin 0.5mg or placebo every night for 14 days or until discharge. The melatonin group had reduced delirium (12%) in comparison to the placebo group (31%; $p=0.014$). Both of these studies suggest that prophylactic administered melatonin has a protective effect on the development of hospitalized delirium in older adults.

This study is important because it provides high level evidence regarding the effect of the amino acid tryptophan on postoperative delirium. Serum amino acids, and in particular tryptophan, have been highlighted as one of the more promising areas of future exploration to both investigate the etiology and potential treatment of delirium.⁹ While the causes of postoperative delirium are multifactorial (including medication usage, the inflammatory response, cholinergic activity, dopamine activation, and glutamate activation), the tryptophan – serotonin - melatonin pathway almost certainly factors into the whether or not delirium occurs in the postoperative setting.³⁶ Completion of clinical trials aimed to modify the delirium relevant pathways is important given the relevance and frequency of this untoward outcome.

There are three main limitations of this study. First, the study patient population underwent substantial surgical stresses (major operations requiring an intensive care unit admission); a fact which may not make the findings of this study relevant to all postoperative surgical

patients. Given that the causes of postoperative delirium are likely multi-factorial, the substantial inflammatory response following these operations may overwhelm any potential for tryptophan and its downstream products to effect the occurrence of delirium. As a result, the findings of this study are likely not applicable to all postoperative patients. Second, oral supplementation of tryptophan may not be optimal. While a statistically significant difference of tryptophan levels was achieved in the study drug group; this difference may not represent the clinically significant difference. The effect of higher dosing of the tryptophan or initiating tryptophan supplementation sooner are not accounted for by this study design. Third, the majority of the patients in this study were male (98%); a fact that represents the demographics of a Veterans Affairs hospital and not a selection bias. The fact that this study included mostly males limits the generalizability of the findings to females. Repeating this study including females may be warranted.

CONCLUSION

In summary, this study provides evidence that tryptophan supplementation does not prevent postoperative delirium in older adults undergoing major elective operation requiring postoperative intensive care unit admission. Future directions of this research may include investigating the protective effect of tryptophan in other clinical settings (e.g., on hospitalized medical patient or postoperative patients admitted to the surgical ward) or to examine the effects of supplementing the downstream products of tryptophan (e.g., melatonin) on the occurrence of delirium.

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Appendix1– Exclusion Criteria Medication List

The exclusion criteria for this study aim to exclude patients who are at high risk for a complication from tryptophan. Subjects taking medications that when combined with tryptophan would risk serotonin syndrome will be excluded. The medications are:

MONOAMINE OXIDASE INHIBITORS

isocarboxazid (Marplan)
phenelzine (Nardil)
tranylcypromine (Parnate)
isoniazid

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

citalopram (Celexa, Cipramil, Emocal, Sepram, Seropram)
escitalopram (Lexapro, Cipralex, Esertia)
fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem)
fluvoxamine (Luvox, Faverin, Dumyrox)
paroxetine (Paxil, Seroxat, Aropax, Deroxat, Rexetin, Xetanor, Paroxat)
sertraline (Zoloft, Lustral, Serlain)
zimeclidine (Zelmid, Normud)

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

venlafaxine (Effexor XR, Effexor)
nefazodone (Serzone)
duloxetine (Cymbalta)
tricyclic antidepressants [amitriptyline (Elavil, Endep, Tryptanol, Trepiline, Amyzol)]
amoxapine (Asendin, Asendis, Defanyl, Demolox, Moxadil)
clomipramine (Anafranil)
desipramine (Norpramin, Pertofrane)
dosulepin hydrochloride (Prothiaden, Thaden)
doxepin (Adapin, Sinequan)
imipramine (Tofranil, Janimine)

nortriptyline (Aventyl, Pamelor)
opipramol (Opipramol-neuraxpharm, Insidon)
protriptyline (Vivactil, Rhotrimine)
trimipramine (Surmontil)]

TRIPTANS

sumatriptan (Imitrex, Imigran)
rizatriptan (Maxalt)
naratriptan (Amerge, Naramig)
zolmitriptan (Zomig)
eletriptan (Relpax)
almotriptan (Axert, Almogran)
frovatriptan (Frova, Migard)

STIMULANTS

Phentermine
Diethylpropion
Amphetamines
substituted amphetamines
sibutramine
methylphenidate
methamphetamine
cocaine

OTHER MEDICATIONS

meperidine (Demorol)
tramadol
Bupropion
St. John's Wort

Figure 1.
Screening, Enrollment and Randomization Flowchart

Table 1

Baseline Characteristics – Pre- and Intra-Operative

	Total Group (n=301)	L-Tryptophan (n=152)	Placebo (n=149)	p-value
Baseline Preoperative Variables				
Age (years)	69±7	69±8	69±7	0.779
Male gender	295 (98%)	99% (150)	97% (145)	0.396
Timed Up and Go (seconds)	12±3	12±3	12±4	0.516
Depression	41% (123)	39% (59)	43% (64)	0.493
Comorbidities (Charlson Index)	2.4±2.0	2.3±1.8	2.5±2.1	0.329
Creatinine (mg/dL)	1.1±0.3 (300)	1.2±0.3	1.1±0.3	0.133
Body Mass Index	28±6	28±6	27±5	0.226
Albumin (gm/dL)	3.8±0.5	3.8±0.5	3.8±0.5	0.100
Hematocrit (%)	41±6	41±6	42±6	0.440
Sodium (mEq/L)	139±3	139±3	139±3	0.549
Potassium (mEq/L)	4.3±0.4	4.3±0.4	4.3±0.4	0.555
ASA Score (3)	83% (249)	81% (123)	85% (126)	0.448
Alcohol Dependence (AUDIT)	1.9±2.5	1.7±2.5	2.0±2.6	0.291
Impaired Cognition:MiniCog 3	31% (94)	31% (47)	32% (47)	0.938
Dependence in 1 ADL	13% (38)	13% (19)	13% (19)	0.947
Having fallen in past 6 months	21% (63)	20% (30)	22% (33)	0.628
Intra-Operative Variables				
Type of Surgery				
Abdominal	39% (118)	47% (56/118)	53% (62/118)	0.515
Non-Cardiac Thoracic	5% (16)	38% (6/16)	63% (10/16)	0.289
Cardiac	42% (126)	41% (63/126)	42% (63/126)	1.000
Vascular	14% (41)	66% (27/41)	34% (14/41)	0.008
General Anesthesia	100% (300)	100% (152)	99% (148)	0.495
OR Time (minutes)	277±110	283±113	270±107	0.302
Blood Loss (mL)	595±994 (175)	578±745	612±1203	0.819
Transfusion in Operating Room	22% (66)	24% (36)	20% (30)	0.457

Acronyms: ASA = American Society of Anesthesiologists; AUDIT = Alcohol Use Disorders Identification Test; ADL = activities of daily living

Table 2

Postoperative Outcomes

	Total Group (n=301)	L-Tryptophan (n=152)	Placebo (n=149)	p-value
Post-Operative Course				
One or more Complications	32% (97)	34% (52)	30% (45)	0.457
Cardiac	2% (5)	2% (3)	1% (2)	0.668
Respiratory	7% (20)	7% (10)	7% (10)	0.999
Renal	1% (2)	1% (1)	1% (1)	0.989
Neurologic	1% (4)	1% (1)	2% (3)	0.305
Infection	13% (38)	14% (21)	11% (17)	0.811
Sepsis	2% (6)	3% (5)	1% (1)	0.104
DVT	1% (3)	1% (2)	1% (1)	0.573
Re-Operation	7% (19)	8% (9)	7% (10)	0.817
Benzodiazepine (% received)	11% (32)	11% (16)	11% (16)	0.952
Haloperidol (% received)	2% (7)	3% (5)	1% (2)	0.262
Pain score (average first 3 days)	3.2±1.6	3.2±1.6	3.3±1.7	0.473
Sleep hours (average first 3dys)	4.5±1.5	4.6±1.5	4.4±1.5	0.138
1 day on ventilator	11% (32)	11% (17)	10% (15)	0.852
Narcotics (average first 3 days) ^a	39±40	38±42	40±38	0.726
ICU Stay (days)	<u>5.0±4.1</u>	<u>5.2±4.1</u>	<u>4.8±4.2</u>	<u>0.749</u>
Hospital Stay (days)	9.9±8.6	10.0±8.4	9.7±8.7	0.695
Mortality				
Hospital Mortality	2% (7)	2% (3)	3% (4)	0.722
30-day Mortality	4% (13)	3% (5)	5% (8)	0.410
6-month Mortality	10% (30)	11% (17)	9% (13)	0.565

^a narcotics reported in milligram equivalents of intravenous morphine. Acronym – ICU = intensive care unit

Table 3**Delirium Outcomes& L-Tryptophan Levels**

	Total Group (n=301)	L-Tryptophan (n=152)	Placebo (n=149)	p-value
Delirium (overall)	39% (116)	40% (61)	37% (55)	0.597
Excitatory delirium	13% (39)	17% (26)	9% (13)	0.172
Hypoactive delirium	26% (77)	23% (35)	28% (42)	0.172
Duration delirium (overall)(days)	2.6±1.7	2.9±1.8	2.4±1.6	0.118
Duration excitatory delirium (days)	3.2±1.8	3.3±1.7	3.1±1.9	0.741
Time to delirium overall (days)	2.0±1.2	2.0±1.1	2.1±1.3	0.696
Time to excitatory delirium (days)	1.8±1.2	1.8±1.2	1.9±1.2	0.797
Tryptophan Biomarkers				
Preoperative				
Tryptophan (umol/L)	42±13 (229)	43±14 (117)	42±13 (112)	0.522
Serotonin (ng/mL)	107±80 (227)	99±81 (114)	115±79 (113)	0.140
Melatonin(pg/mL)	20±36 (215)	20±31 (113)	19±41 (102)	0.987
Postoperative day 2				
Tryptophan(umol/L)	53±24 (193)	65±26 (99)	41±15 (94)	<0.001
Serotonin (ng/mL)	79±65 (193)	76±75 (99)	83±54 (94)	0.483
Melatonin (pg/mL)	66±114 (184)	78±145 (97)	52±63 (87)	0.126

Acronym: postop = postoperative

Table 4**Study Drug Data**

	Total Group (n=301)	L-Tryptophan (n=152)	Placebo (n=149)	p-value
Study Drug Administration				
Total doses of study drug	2016 doses	1010 doses	1006 doses	
Missed Doses (total)	6% (122)	6% (58)	6% (64)	0.576
Patient NPO by clinical team	2% (43)	2% (20)	2% (23)	0.621
Dose not available	2% (33)	1% (11)	2% (22)	0.055
Patient request to miss dose	1% (22)	1% (14)	1% (8)	0.284
Patient nauseated	1% (19)	1% (10)	1% (9)	1.000
Other ^a	<1% (5)	<1% (3)	<1% (2)	1.000
Total Patient with Study Drug Side Effects				
No study drug side effect	88% (265)	85% (129)	91% (136)	0.373
Nausea	10% (31)	12% (18)	9% (13)	0.449
Bad taste	2% (5)	3% (5)	0	0.061
Eosinophilia (%)	0.7±1.4	0.6±0.8	0.8±1.7	0.189

^a Other reasons to miss doses of study drug or placebo included: acute renal failure (2), eosinophilia (1), at provider request (2).

Acronyms: NPO = nil per os