The risk factors of trigeminocardiac reflex caused by Onyx embolization during cerebrovascular intervention operation

Zhaochu Sun
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
https://orcid.org/0000-0002-8663-3321
Piplu Bhuiyan
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Hua Lu
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Yanning Qian (yanningqian@njmu.edu.cn)
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Hang Xiao
Nanjing Medical University

Research Article

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Abstract

Background

Trigeminocardiac reflex (TCR) is a brainstem reflexive response of hemodynamic instability during surgery. However, few risk factor analysis and management strategies of TCR have been highlighted in the literature. The purpose of this study was to demonstrate the risk factors for Onyx embolization during cerebrovascular intervention operation so as to optimize perioperative management and reduce the incidence of TCR.

Methods

We performed a retrospective study on consecutive patients with Onyx embolization over a 4-years period. According to whether TCR episode, they were divided into TCR group and control group. Cases and controls were compared regarding patient characteristics, comorbidities, hemodynamics and complications. We also constructed several multivariable regression models to analyze the risk factors.

Results

Among 195 identified patients, 27 patients (13.8%) occurred TCR. During DMSO/Onyx injection, HR and MAP were much lower in the TCR group than control group ($P < 0.01$). Notably, on univariable analysis, the patients with dural arteriovenous fistula (DAVF) and middle meningeal artery being affected was associated with a higher incidence of TCR ($P < 0.01$). On multivariable analysis, we also found that significant predictors of TCR were DAVF (OR = 12.78; 95%CI [3.57–45.68]), CCF (OR = 7.65; 95%CI [1.64–35.65]), the lesion which supplied by the middle meningeal artery (OR = 4.24; 95%CI [1.67–10.73]), and bradycardia before embolization (OR = 2.55; 95%CI [1.08–5.99]).

Conclusion

This study demonstrated that DAVF, CCF, and middle meningeal artery embolism may the risk factors for intraoperative TCR episode during Onyx endovascular embolization. Therefore, it is worth further study to take appropriate measures to block TCR-related risk factors during endovascular embolization.

Trial registration:

ChiCTR, ChiCTR2000038839; Registered 5 October 2020.

Introduction

Trigeminocardiac reflex (TCR) is a unique brain stem reflex that manifests as the sudden onset of hemodynamic perturbation in heart rate and blood pressure as a result of stimulation of any branches of the trigeminal nerve [1]. TCR has been described during intracranial, maxillofacial, ophthalmic surgery, endovascular treatment of intracranial dural arteriovenous, and carotid-cavernous fistulas as well as radiofrequency lesioning of the trigeminal ganglion [2].

In recent years, with the development of neurointerventional technology, the treatment of Onyx embolization has gradually become an independent and important measures for the cerebrovascular malformation. This technique achieves the purpose of blood flow redistribution by blocking blood supply and occluding arteriovenous fistula, which has been clinically confirmed [3]. However, with the wide application of Onyx in interventional operation, its common complications and potential risks should not be ignored. Onyx embolization in cerebrovascular interventional surgery might trigger TCR, leading to severe hemodynamic fluctuations and even cardiac arrest [4–9]. In addition, the occurrence of TCR is unpredictable, and there is no appropriate prophylactic approaches to prevent. Therefore, TCR is beginning to reactivation in our field of vision, which needs to be paid enough attention.

Due to its relatively low incidence and high potential risk, there is no clear consensus on prevention or treatment of TCR, therefore, we need to recognize this phenomenon as soon as possible. In this study, we aimed to retrospectively investigated the incidence and related risk factors of TCR during the treatment of cerebrovascular embolization with Onyx to guide clinical practice.

Materials And Methods

This retrospective observational cohort study was approved by the Institutional Review Board (IRB) of The First Affiliated Hospital of Nanjing Medical University/Jiangsu Province Hospital (JSPH; Jiangsu, China; IRB approval number: 2020-SR-312), and registered on Chinese Clinical Trial Register (chictr.org.cn ChiCTR2000038839; October 5, 2020). Considering the retrospective design of this study, the requirement for informed consent was waived by the IRB.

Participants and Study Design

This study utilised data stored and managed in the electronic medical record system of JSPH on 215 patients who were decided to perform Onyx embolization operation under general anesthesia by neurosurgeon, from January 2016 to May 2020 at a single academic institution. Patients < 18 years old were excluded from the study. Similarly, patients with preoperative confusion, communication difficulties were not eligible. Lastly, we excluded patients with severe complications unrelated to cerebrovascular embolism occurred during perioperative period. According to whether TCR episode during the operation, they were divided into TCR group (T group) and control group (C group). In all cases, the archived cases and anesthetic records were reviewed in detail, and the data were true and reliable. All the cases for the study period were screened by a group of medical record technicians in the medical informatics team who were not informed of the purpose of this study.

Monitoring and Anesthesia

All patients were performed with standardization of anesthesia induction and maintenance, intraoperative anesthetic management was performed with continuous monitoring of peripheral capillary oxygen saturation, electrocardiography (ECG), arterial blood pressure, end-tidal carbon dioxide partial pressure (PetCO2) and Bispectral index (BIS). Anesthesia was induced with midazolam 0.05 mg/kg, fentanyl 3 mg/kg, propofol 2 mg/kg, cisatracurium 0.15mg/kg. Mechanical ventilation (Drager, Fabius-Plus, Germany) was used during the operation to keep PetCO2 at 30–45 mmHg. All patients received 1%-2% sevoflurane and 2–5 mg/kg·h propofol for anesthesia maintenance until the end of operation, and 0.1 mg/kg·h cisatracurium for muscle relaxation to half an hour before the end. The depth of anesthesia was guided by BIS < 60 to prevent intraoperative awareness.

Variables and Outcomes

Perioperative variables were ascertained from patient records. The following data were recorded: patient age, sex, Body Mass Index (BMI), comorbidities, protopathy, supplying vessels, PetCO2, BIS value (record per 5 minutes during embolization), hemodynamic indexes (baseline, before embolization, embolization and end of procedure) and the use of atropine, what's more the postoperative outcomes. For the purposes of this study, TCR was defined as the sudden onset of bradycardia triggered by stimulation of the trigeminal nerve and its anatomic branches. The bradycardia is characterized by a reduction in HR of 20% or more from the baseline, and/or asystole. Change in MAP is an optional criterion for the definition of TCR [10–11], but not included as part of the TCR definition in this study.

Statistical Analysis

All the statistical analysis was performed with SPSS 23.0 (IBM Software Inc., USA). Categorical variables were presented using numbers with percentages and were analyzed with chi-square test or Fisher's exact test, whereas the continuous variables were expressed as mean ± standard deviation, and were compared with the Student's t-test for unpaired samples when a normal deviation was assumed. Univariate and stepwise multivariate logistic regression analysis were performed to determine the risk factors of TCR episode. All clinically sensible covariates were included in the model. For all analysis, a P value of < 0.05 was considered statistically significant.

Results

Patient Characteristics

We identified 215 patients who required endovascular embolization therapy with Onyx under general anesthesia during the study period. Of these, 11 patients with preoperative disturbance of consciousness, and 9 children younger than 18 years were excluded. Therefore, our final study cohort included 195 patients who fulfilled our selection criteria (Fig. 1).

The demographic and clinical characteristics over the entire cohort are presented in detail in Table 1. The mean (SD) age of our cohort was 45.3 (15.1) years. Gender distribution was 121 male (62.1%) and 74 female (37.9%) patients. In terms of comorbidities, hypertension was present in 20.5% of patients, diabetes mellitus in 6.2%, bradycardia in 11.8%, and the history of cerebral hemorrhage in 36.9%. Regarding preoperative diagnosis, 93 patients (47.7%) were diagnosed with arteriovenous malformation (AVM), 55 (28.2%) with dural arteriovenous fistula (DAVF), 16 (8.2%) with carotid-cavernous fistula (CCF), and 31 (15.9%) with intracranial tumors.

Table 1
Baseline Characteristics

Variable	**Total, % (N = 195)**
Age, mean (SD)	45.3 ± 15.1
Sex	
Male	121(62.1)
Female	74(37.9)
BMI(Kg/m2)	23.4 ± 2.9
Comorbidity	
Hypertension	40(20.5)
Diabetes mellitus	12(6.2)
Bradycardia	23(11.8)
History of cerebral hemorrhage	72(36.9)
Protopathy	
AVM	93(47.7)
DAVF	55 (28.2)
CCF	16 (8.2)
Intracranial tumors	31 (15.9)
Supplying vessels	
Meningeal artery	60(30.8)
Middle meningeal artery	52(26.7)
Cerebral artery	129(66.2)
Anticholinergics therapy	10(5.1)

Abbreviations: N, number of patients; IQR, interquartile range; BMI, body mass index; AVM, arteriovenous malformation; DAVF, dural arteriovenous fistula; CCF, carotid-cavernous fistula.

Demographics

As shown in Table 2, 27(13.8%) patients developed TCR in varying degrees, of which 4 patients suffered cardiac arrest, at the time of DMSO/Onyx injection. The TCR and control group were similar to one another with regard to the matched variables, including age, sex, BMI, and comorbidity.

Table 2
Characteristics of Patients Exhibiting with or without TCR

Variable	TCR (N = 27)	Control (N = 168)	*P*-Value
Age (yr)	47.7 ± 13.7	44.9 ± 15.3	0.38
Sex			
Male	19(70.4)	102(59.4)	0.34
Female	8(29.6)	66(40.6)	0.34
BMI(Kg/m2)	23.8 ± 2.9	23.3 ± 2.9	0.43
Comorbidity			
Hypertension	7(25.9)	33(19.6)	0.45
Diabetes mellitus	2(7.4)	10(6.0)	0.78
Bradycardia	3(11.1)	20(11.9)	0.91
History of cerebral hemorrhage	8(29.6)	64(38.1)	0.40
Protopathy			
AVM	2(7.4)	91(54.2)	< 0.01
DAVF	21(77.8)	34(20.2)	< 0.01
CCF	2(7.4)	14(8.3)	0.87
Intracranial tumors	2(7.4)	29(17.3)	0.16
Supplying vessels			
Middle meningeal artery	19(70.4)	33(19.6)	< 0.01
Cerebral artery	3(11.1)	126(75.0)	< 0.01
HR			
Baseline	75.1 ± 12.6	76.1 ± 11.5	0.67
Before embolization	63.5 ± 8.7	65.7 ± 8.6	0.23
Embolization	38.3 ± 17.1	65.4 ± 10.6	< 0.01
End of procedure	68.6 ± 10.2	70.3 ± 9.6	0.39
MAP			

N, number of patients; BMI, body mass index; AVM, arteriovenous malformation; DAVF, dural arteriovenous fistula; CCF, carotid-cavernous fistula; HR, heart rate; MAP, mean arterial pressure.

*P < 0 .05.

Variable	TCR (N = 27)	Control (N = 168)	*P*-Value
Baseline	96.1 ± 12.2	93.5 ± 10.3	0.24
Before embolization	82.0 ± 9.9	81.6 ± 8.4	0.82
Embolization	74.4 ± 38.8	86.3 ± 12.5	< 0.01
End of procedure	89.5 ± 8.0	86.2 ± 8.5	0.06
Bradycardia (before embolization)	10(37.0)	44(26.2)	0.24
N, number of patients; BMI, body mass index; AVM, arteriovenous malformation; DAVF, dural arteriovenous fistula; CCF, carotid-cavernous fistula; HR, heart rate; MAP, mean arterial pressure.			
*P < 0 .05.			

Among TCR group, 21 patients were diagnosed with DAVF, 2 with CCF, 2 with AVM, and 2 with intracranial tumors. On univariable analysis, TCR cases had a higher prevalence of DAVF (77.8% vs 20.2%; P < 0.01) and middle meningeal artery embolisation (70.4% vs 19.6%; P < 0.01). According to hemodynamics, during DMSO/Onyx injection, HR was much slower in the TCR group than control group (38.3 ± 17.1 vs 65.4 ± 10.6 bpm, P < 0.01), and MAP was lower in TCR group (74.4 ± 38.8 vs 86.3 ± 12.5 mmHg, P < 0.01).

On multivariable analysis (Table 3), we found that significant predictors of TCR were DAVF (OR = 12.78; 95% CI [3.57–45.68]), CCF (OR = 7.65; 95% CI [1.64–35.65]), the lesion which supplied by the middle meningeal artery (OR = 4.24; 95% CI [1.67–10.73]), and the patients who presented bradycardia before embolization (OR = 2.55; 95% CI [1.08–5.99]).

Table 3
Multivariate Logistic Regression Analysis about TCR Episode

		95% CI		
Predictor	OR	Lower	Upper	*P*-Value
Protopathy				
DAVF	12.78	3.57	45.68	< 0.01
CCF	7.65	1.64	35.65	0.01
Intracranial tumors	1.54	0.31	7.76	0.60
AVM	1	-	-	-
Supplying vessels				
Middle meningeal artery	4.24	1.67	10.73	< 0.01
Cerebral artery	1	-	-	-
Bradycardia (before embolization)	2.55	1.08	5.99	0.03

AVM, arteriovenous malformation; DAVF, dural arteriovenous fistula; CCF, carotid-cavernous fistula; OR, odds ratio; CI, confidence interval.

*P < 0 .05.

Table 4 shows the patients with significant hemodynamic fluctuations. Intraoperatively, bradycardia occurs during TCR episode, however, blood pressure may appear to be either lower or higher. 13 patients presented with hypotension, while 14 patients with hypertension. Among them, whose embolized vessel is the middle meningeal artery is more likely to present with cardiac arrest and hypotension when TCR episode. In addition, this study results also showed that 16 patients just experienced a 20% increase in blood pressure and no significant decrease in heart rate during the process of embolization. Whereas, we did not find patients presenting with a simple hypotension.

Table 4
Description of patients with significant hemodynamic fluctuations

	Total	DAVF	Other protopathy	Middle meningeal artery	Other vessels
Heart arrest	4	2(50)	2(50)	3(75)	1(25)
HR decrease > 20%	27	21(77.8)	6(22.2)	19(70.4)	8(29.6)
HR decrease > 20% with MAP decrease	13	9(69.2)	4(30.8)	11(84.6)	2(15.4)
HR decrease > 20% with MAP increase	14	12(85.7)	2(14.3)	8(57.1)	6(42.9)
HR, heart rate; MAP, mean arterial pressure.					

Prognosis

The composite adverse events occurred in 4 of 27 (14.8%) patients in the TCR group and in 39 of 168 (23.2%) of the patients in the control group (P > 0.05). The incidence of postoperative dizziness, headache, PONV, and muscle weakness were quite similar in two groups (P > 0.05) (Table 5).

Table 5
Outcome Analyses and Adverse Events

Variable	TCR (N = 27)	Control (N = 168)	*P*-Value
Composite adverse events	4 (14.8)	39 (23.2)	0.48
Dizziness	2(7.4)	27(16.1)	0.38
Headache	2(7.4)	21(12.5)	0.66
PONV	1(3.7)	8(4.8)	1.0
Muscle weakness	1(3.7)	4(2.4)	1.0
Other severe unexpected events	1(3.7)	11(6.5)	0.89
The components of the composite adverse events (within the first 24 h after operation) were dizziness, headache, PONV (Post Operative Nausea and Vomiting), muscle weakness, and other severe unexpected events (aphasia, hypopsia, etc.)			

Discussion

The TCR is a critical cardiovascular event found in several surgical procedures involving a structure innervated by the trigeminal nerve. TCR occurs during treatment of endovascular embolization, which results in an intense autonomic disturbance of the heart that manifests as the sudden onset of bradycardia, hypotension, arrhythmias and even heart arrest. Sudden hemodynamic fluctuations may affect the course of surgery and patient prognosis. Therefore, TCR and related risk factors have gained much interest during recent years. In this study, we have analyzed, the relation between DAVF and TCR occurrence highlight a strong association. We also found a higher pooled risk for embolization vessel supplied by the middle meningeal artery for hypotension and occurrence of asystole during TCR, suggesting a more severe reflex variant under these conditions.

The physiological mechanism of TCR is that signals triggered by either peripheral or central stimulation on the sensory nerve endings of the trigeminal nerve are relayed to the sensory nucleus of the trigeminal nerve. This afferent pathway continues along the short internuncial nerve fibers in the reticular formation to connect with the efferent pathway in the motor nucleus of vagus nerve and nucleus ambiguus. The fibers of vagus or sympathetic nerves end in the myocardium, leading to autonomic changes that usually manifests as a negative chronotropy [12]. However, there are two major subtypes of peripheral or central TCR. Previous studies have suggested that peripheral stimulation of the trigeminal nerve co-actives vagal and sympathetic nerves, resulting in both hypertension (peripheral vasoconstriction) and bradycardia [13]. By contrast, central stimulation may cause hypotension and bradycardia by generating profound activation of the cardiac vagal branch and specific inhibition of the inferior cardiac sympathetic nerve [14].

In this study, we observed that all the TCR patients presented with heart rate deceleration > 20%, or even cardiac arrest, but just 13 patients experienced blood pressure reduction. On the contrary, 14 patients presented with blood pressure increase. Therefore, we suggest that central stimulant from chemical agents and distinct endovascular embolization might share the common efferent pathway for vagus activation, but the induce of inhibitory or promotive effect on efferent sympathetic pathway may co-existence in the process of central TCR, which depends on the site of stimulation. Hypertension may be associated with a greater susceptibility of sympathetic nerve stimulation, while the occurrence of hypotension is partly in a heart-rate-dependent manner, with significant blood pressure reduction when the heart rate is too slow. The low incidence of hypotension in this study may be related to our team's close monitoring of intraoperative hemodynamic changes, which usually prevented the continued deterioration of TCR.

In this cohort, we found that in the TCR group, the patients with protopathy of DAVF accounted for 77.8%, and the patients whose supplying vessel was the middle meningeal artery accounted for 70.4%, which was significantly higher than that in the control group. Therefore, we suspected that the patients with DAVF or middle meningeal artery embolization are the risk factors for TCR episode during DMSO or Onyx injection. These results are consistent with the previous case reports that TCR occurs mainly in patients with DAVF during cerebrovascular interventional embolization operation.

DAVFs are abnormal connections between dural arteries and venous sinuses. The dura mater is innervated in part by branches of the trigeminal nerve and receives vascular supply from the meningeal artery as well as meningeal branches of the occipital artery [15]. These vessels are primarily involved in the blood supply to the sensory area of the trigeminal nerve. Therefore, when the meningeal artery receives mechanical or chemical stimulation, trigeminal nerve excitability increases, leading to the episode of TCR. To some extent, these results support the anatomically specific triggering of TCR. Anesthesiologists and neurosurgeons should be alert to the occurrence of TCR during DAVF embolization.

Studies have confirmed that Onyx has no effect on hemodynamics by itself [16]. However, mechanical stimulation of the trigeminal nerve during DMSO or Onyx injection is an essential inducement of TCR, and this effect is closely related to the dose and rate of injection [17]. Experts recommend that the injection rate of both DMSO and Onyx should not exceed 0.1 ml/min [18]. In this study, all procedures were performed by the same experienced neurosurgeon. Therefore, it seems that we can ignore the effect of injection speed on this study.

The occurrence of TCR is challenging to predict, and there is no precise detection index. Currently, preventive measures for TCR mainly include the use of anticholinergic drugs to reduce vagal excitability and increase the heart rate [19]. However, experts considered that preemptive administration of anticholinergics for the prevention of TCR may be ineffective. It has been observed that bradycardia and hypotension in TCR includes both excessive activation of vagal and inhibition of adrenergic vaso-constriction after electrical stimulation of the spinal trigeminal tract and trigeminal nuclear complex [20]. Atropine can only block the cholinergic fibers, yet cannot completely prevent bradycardia or hypotension. In this study, we also found that some patients often showed MAP increasing during embolization treatment, and atropine may increase the risk of hypertension while increasing the heart rate. In addition, atropine is at risk of refractory arrhythmia, so prophylactic use is not recommended [21]. The results of this study showed that although there was no significant difference in HR between the TCR group and control group, preoperatively and before embolization, however, multivariate logistic regression analysis showed that bradycardia before embolization was a risk factor for TCR. Therefore, it may be necessary to prophylactically correct bradycardia before embolization in high-risk patients.

In view of the large number of similar TCR events, the recognition and treatment of TCR has become increasingly adequate. The surgeon should first be informed to discontinue the procedure once TCR has occurred, resulting in a deterioration in hemodynamics. Withdrawal of stimulation usually reverses this phenomenon immediately, without the need for anticholinergic drugs. For refractory bradycardia and hypotension, anticholinergic agents such as epinephrine or atropine should be initiated. Furthermore, we need to reassess and increase the depth of anesthesia. A meta-analysis [22] showed that lighter anesthesia (CSI > 60) were associated with a 1.2-fold increased incidence of bradycardia and a 4.5-fold increased risk of cardiac arrest than deeper anesthesia (CSI < 40). In this study, all patients had moderate anesthesia depth, and there was no significant difference in BIS value between the two groups. During operation 4 patients occurred cardiac arrest which resumed spontaneous circulation after discontinuation of the procedure and administration of atropine or a small dose of epinephrine. In addition, 6 patients with recurrent HR < 40 bpm were given atropine 0.5mg, and the TCR was successfully corrected. However, the incidence of postoperative adverse events were similar between the two groups, which may be mainly attributed to the in-depth understanding of TCR and timely treatment.

The limitation of this study is being a single-centered study with a relatively limited sample size and potential bias in patient selection. Meanwhile, this study is a retrospective study, in which only BIS values were used as the evaluation index for anesthesia depth. It is difficult to track the real-time blood concentration of various anesthetics, and it is impossible to exclude the influence of drugs on TCR episode.

In summary, the TCR episode may due to chemical stimulus of DMSO and Onyx injection, leading to a significant decrease in HR under a standardized anesthetic protocol. This study confirms that patients with DAVF, CCF and middle meningeal artery embolism are the risk factors for TCR during Onyx endovascular embolization. Therefore, anesthesiologists and neurosurgeons should strengthen the identification of TCR risk factors, and strive to achieve early prevention and treatment to reduce the incidence of TCR-related adverse events.

Abbreviations

BMI
Body mass index
AVM
Arteriovenous malformation
DAVF
Dural arteriovenous fistula
CCF
Carotid-cavernous fistula
HR
Heart rate
MAP
Mean arterial pressure
PetCO2
End-tidal carbon dioxide partial pressure
BIS
Bispectral index
CSI
Cerebral state index.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of Jiangsu Province Hospital (JSPH 2020-SR-312) and the requirement for written informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors’ Contributors

YNQ, ZCS: study concept, literature review, manuscript preparation and revision. PB, HL: data collection, statistic analysis. HX: study concept, critical review, manuscript revision.

All other authors provided substantial critical review and revision of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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Figures

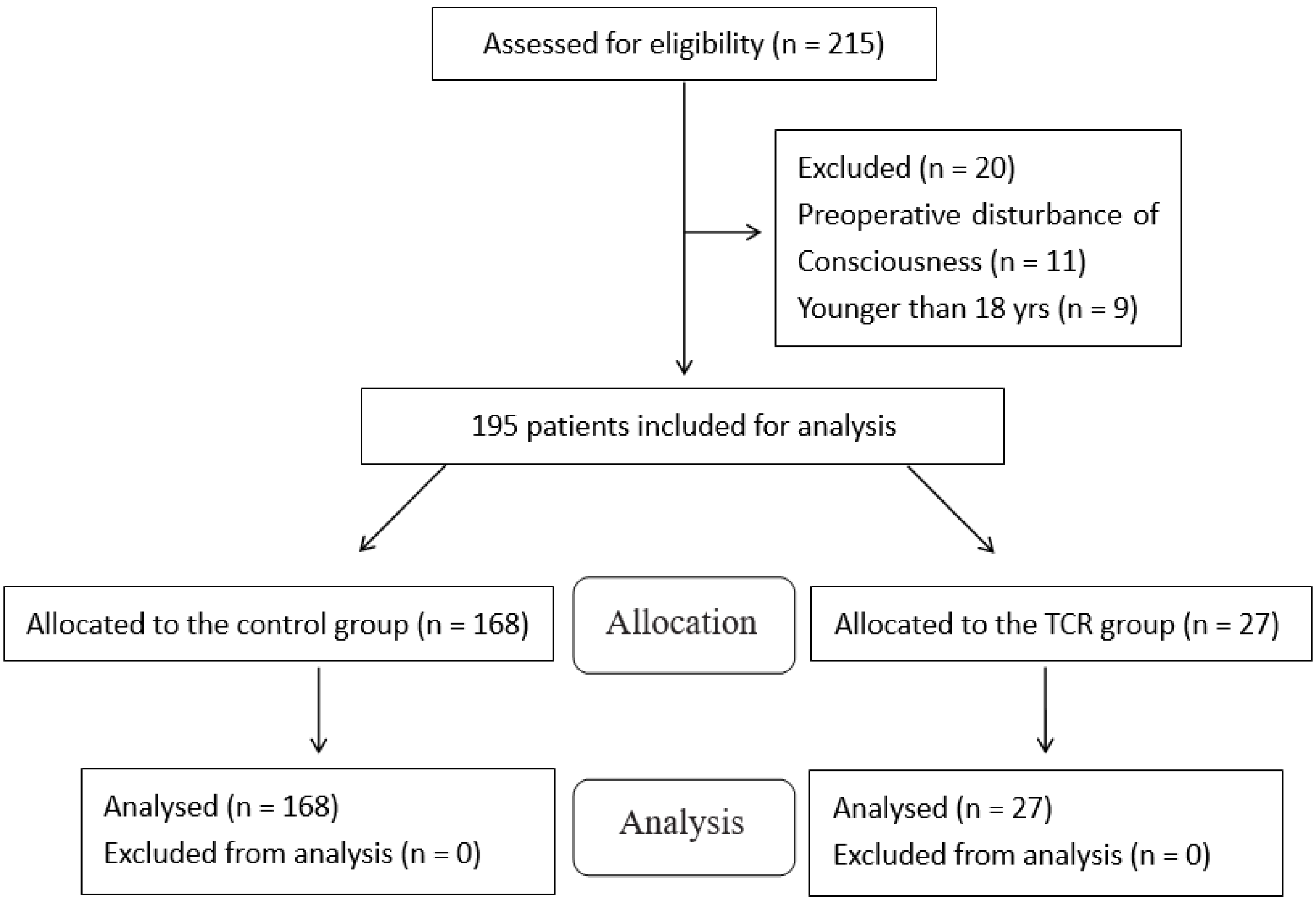

Figure 1

Study Flow Chart.