Effect of Administration of Tranexamic Acid on Blood Loss and Transfusion Requirements in Children Undergoing Posterior Fossa Tumor Excision: A Retrospective Cohort Study

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Abstract

Background

Surgical resection of posterior fossa tumors (PFT) in the pediatric age group often results in significant intraoperative blood loss. The primary objective was to assess the effect of tranexamic acid (TXA) on blood loss and transfusion requirement in pediatrics undergoing excision of PFTs.

Methods: In this retrospective study, all pediatric patients ≤18 years, who underwent PFT resection over a period of 7 years were included. The patient and surgical characteristics estimated blood loss (EBL), the need for blood and blood product transfusion, use of crystalloids, vasopressors, and any adverse events like seizures and thromboembolic events were recorded and compared between Group A who received TXA and Group B who did not.

Results:

The study included 50 patients, out of which 36 belonged to Group A and 14 to Group B. The median age was 8 years (IQR, 2-17) and the mean BMI was 16.46±4.11 kg/m^2. The mean EBL was 224.29±110.36 ml in Group A (n=36) and 362±180.11 ml in Group B (n=14), (p-= 0.007). The intraoperative volume of crystalloid use was significantly higher in Group B (p= 0.04). The requirement of blood and blood product transfusion was similar between the groups, but the volume of blood transfusion per kg body weight was higher in Group B, 8.3 (IQR, 6.7-11.1) ml/kg versus 10.5 (IQR, 8.1-16.1) ml/kg in group A (p-value 0.3) The rates of complications noted in the form of seizures and thromboembolic events were comparable.

Conclusion:

The use of TXA in the pediatric population undergoing PFT resection aids in reducing blood loss during the surgery without increasing complications.

Introduction

Maximal safe surgical resection is the primary goal of surgery in pediatrics with midline posterior fossa tumors (PFTs) [1]. Posterior fossa surgeries can be associated with significant bleeding encountered during craniotomy, dural opening (from the occipital or marginal sinus), and tumor resection. Massive blood loss can lead to hemodynamic instability and coagulopathy, and hence blood conservation strategies need to be employed whenever feasible [2, 3]. Reducing the magnitude of blood loss can effectively aid in more complete tumor resection. Certain blood conservation techniques like preoperative autologous blood donation and acute normovolaemic haemodilution may not be feasible in the pediatric age group due to the need for patient cooperation and a small circulating blood volume [4, 5].

There has been a renewed interest in the use of tranexamic acid (TXA) in various neurosurgical settings like trauma, subarachnoid haemorrhage, tumor resection and spine procedures.[6] Recent studies in adults demonstrate its effectiveness in the reduction of blood loss, the requirement of blood transfusion and achievement of better haemostasis during intracranial tumor resection, with minimal side effects [7–9].

In the pediatric population, intraoperative TXA administration has been associated with a reduction in blood loss and the requirement of allogeneic blood transfusion during calvarial vault remodelling for craniosynostosis and scoliosis correction [10–19]. Though there is frequent use of TXA as a blood conservation strategy in pediatric patients undergoing PFT resection (personal communication), there is a paucity of data regarding its efficacy and safety profile [20]. There are no studies to our knowledge regarding the use of TXA for PFTs in the pediatric population.

The primary objective of this study was to determine the efficacy of TXA in reducing intraoperative blood loss during PFT resection in pediatrics. The secondary objective was to assess the need for blood and blood product transfusion, intraoperative use of crystalloids, use of vasopressors, and adverse events with the use of TXA.

Material And Methods

After Institutional Ethics Committee approval (IRB: 11456), a retrospective review of patients ≤ 18 years who underwent excision of predominantly solid intra axial tumors of the vermis or fourth ventricle between January 2010 to January 2017 by a single neurosurgical

unit, was done. Patients who underwent < 50% excision of tumor and biopsy and those with predominantly cystic tumors were excluded. Patients whose records lacked complete information regarding any of the variables or outcome measures were also excluded.

Protocol for the administration of TXA

T was administered intravenously as a loading dose of 10–15 mg/kg over a period of 20 minutes before scalp incision, followed by a maintenance dose of 3–5 mg/kg/hr every three hours, until skin closure.

Patients

Patients in Group A (n = 36) received TXA as per the protocol outlined above. Those in Group B (n = 14) consisted of consecutive historical controls who underwent excision of PFT before initiation of the practice of administering TXA in our institute.

Variables and Outcome measures

Data were retrospectively collected from the anesthesia records, operative notes, postoperative intensive care unit (ICU) ward records, and inpatient records. The volume of blood loss was estimated by the anaesthesiologist by visual inspection of the operative field, surgical suction bottles and the volume of blood in surgical drapes [9]. Requirement of vasopressors need for blood and blood product transfusion intraoperatively and postoperatively, intraoperative haematocrit/ haemoglobin levels on arterial blood gas and haemoglobin levels on the first postoperative day were noted.

The primary outcome was to compare the observed blood loss between Group A and B patients. The secondary outcomes were to compare the need for blood transfusion, the use of crystalloids, the requirement of vasopressors, the difference between the preoperative and postoperative Hb, and adverse events namely seizures and thromboembolic events between the two groups.

Statistical analysis

Summary data were presented as mean (standard deviation, SD) for continuous variables and categorical variables as numbers and percentages. The characteristics of patients were compared using a t-test for continuous data and categorical data were compared using Chi-square/Fisher's exact test as appropriate. Statistical significance was defined as $p < 0.05$. All analyses were performed using SPSS v25.

Results

Baseline characteristics

There were 36 patients in group A and 14 in group B. The flow of patients in the study has been demonstrated in Fig. 1. There were 35 males. The mean BMI was 16.5 ± 4.1 kg/m^2. The median age was 8 years (IQR, 2–17). The demographic characteristics, pathology of the tumor, tumor size and surgery-related factors were similar in both groups as summarized in Table 1.

Table 1
shows the patient and surgery-related variables between Group A and Group B

Variables (Mean ± SD)	GROUP A (N = 36)	GROUP B (N = 14)	P-VALUE
Age (years)	8.3 ± 4	7.8 ± 5	0.68
Weight(kg)	23.5 ± 10.5	27.5 ± 14.9	0.35
BMI	15.6 ± 3.5	17.9 ± 4.8	0.12
Sex (Male: Female)	24:1	11:3	0.72
Tumor size (cm)	4.7 ± 1.1	4.7 ± 2.4	0.98
Tumour pathology(%)	22(62.8)	7(50)	0.35
Medulloblastoma	5(14.3)	1(7.1)	
Ependymoma:	8(22.9)	6(42.9)	
Others			
Preop GCS score	14.7 ± 1.2	14.7 ± 0.9	0.47
Re-surgery	5(13.9%)	0	
Preop Hb	13.2 ± 1.2	13.5 ± 1.2	0.94
Extent of Tumor resection (%)	21(58.3)	10(71%)	
Gross total	15 (41.7)	4(29%)	
Subtotal			
Duration of surgery (hours)	5.7 ± 1.95	5.3 ± 0.9	0.68
Postop days in hospital (days)	6.1 ± 4.4	5.1 ± 2.4	0.49

BMI = body mass index, Hb = hemoglobin, GCS = Glasgow coma scale. Group A = patients who received Tranexamic Acid, Group B = patients who did not received Tranexamic Acid. p value < 0.05 is considered to be significant.

Outcome measures

The estimated blood loss was 224.3 ± 110.4 ml in Group A, which was significantly lower than that in Group B (362 ± 180.1 ml) (p = 0.007). The blood loss estimated with respect to body weight was 11.8 ± 7.7 ml/kg in group A and 16.5 ± 13.7 ml/kg in Group B. The estimated blood volume lost (EBV lost) was 12% in Group A and 20% in Group B. The volume of blood transfused was found to be more in Group B (Table 2). The blood volume transfused in terms of weight was 8.3 (IQR, 6.7–11.1) ml/kg in Group A and 10.5 (IQR, 8.1–16.1) ml/kg in Group B. The volume of crystalloids used intraoperatively was significantly higher in Group B (1495 ± 16 ml) compared to Group A (911.82 ± 396.2 ml) (p = 0.04) (Table 2).

Table 2
describes the comparison of intraoperative blood loss and transfusion requirements between Group A and Group B

Parameter	GROUP A (N = 36)	GROUP B (N = 14)	P-VALUE
Blood loss (ml)	224.3 ± 110.4	362 ± 180.1	0.007
Blood loss per kg body weight (ml/kg)	11.8 ± 7.7	16.5 ± 13.7	0.19
% Estimated Blood volume lost	12%	20%	
Crystalloid use (ml)	911.8 ± 396.2	1495 ± 16	0.004
Number of patients requiring Blood Transfusion (%)	21 (58.3%)	7 (50%)	0.59
Volume of blood transfused (ml)	231.5 ± 174.7	254.4 ± 75.8	0.21
Mean ± SD	150 (125–275)	230 (190–325)	
Median (IQR)			
Blood volume transfused per kg body weight (ml/kg)	11.4 ± 8.5	12.2 ± 6.2	0.3
Mean ± SD	8.3 (6.7–11.1)	10.5 (8.1–16.1)	
Median (IQR)			
Number of patients requiring Blood products (%)	1 (8.3%)	2 (28.6%)	0.24
Number of patients requiring FFP	1	2	0.2
Number of patients requiring PRC	0	1	1
Number of patients requiring cryoprecipitate	1	2	1
Number of patients requiring colloid (%)	12 (33.3%)	6 (42.9%)	0.52
Number of patients requiring inotropes(%)	11 (30.6%)	3 (21.4%)	0.51
Intraop Hb (g/dl)	9.63 ± 1.65	10.48 ± 1.42	0.18
Postop Hb (g/dl)	11.36 ± 1.78	11.23 ± 2.00	0.83
Urine output (ml)	519 ± 34.6	608.33 ± 32	0.82

Hb = hemoglobin, FFP = fresh frozen plasma, PRC = platelet rich concentrate, Group A = patients who received Tranexamic Acid, Group B = patients who did not received Tranexamic Acid. p value < 0.05 is considered to be significant.

The requirement of blood, blood product transfusion, the requirement of vasopressors, urine output, and preoperative and postoperative haemoglobin levels were found to be similar between the groups (Table 2). Two patients were reported to have seizures in the immediate postoperative period, both of whom belonged to Group B. None of the patients had thromboembolic episodes in the perioperative period. The total length of ICU and hospital stay were similar between the groups.

Discussion

Blood conservation strategies in posterior fossa tumor surgeries

Blood loss is a major concern in pediatrics undergoing excision of PFTs. The most common pediatric posterior fossa tumors include astrocytomas, medulloblastomas, ependymomas, and brainstem gliomas [21]. In our study, medulloblastoma was found to be the most common tumor in both study groups. Medulloblastoma, the most common tumor of the fourth ventricle in childhood, is usually a highly vascular tumor with a lack of a clear-cut boundary with the site of attachment [1]. Resection of such tumors can lead to hemodynamic instability requiring inotropic support and the use of blood and blood product transfusion, all of which can add to postoperative morbidity [22, 23]. With advances made in neurosurgery and neuroanesthesia, more surgeons are attempting complete resection of tumors as it has a definite bearing on overall survival [1]. Both insidious and acute blood loss results during tumor resection. Management of blood loss especially in pediatric patients undergoing PFT resection in the prone position is one of the most challenging aspects of anaesthetic

management. Although many blood conservation strategies have been investigated to mitigate blood loss, they cannot be routinely employed in pediatric patients [4].

TXA in neurosurgery

TXA, an effective antifibrinolytic has been proven to be effective in reducing blood loss in diverse surgical settings. Over the last five years, TXA is being administered routinely post-induction in pediatrics undergoing excision of posterior fossa tumors (personal communication). This stems from the data on TXA being proven in randomized trials to reduce blood loss during surgery for craniosynostosis correction [11, 13]. Studies have also shown the beneficial effect of TXA in the pediatric population undergoing cardiac procedures [24] and spine surgeries held, [18, 19] without any significant adverse events.

Although there have been many studies on the use of TXA in the pediatric population as summarised in Table 3, our study is the largest retrospective cohort reporting the benefit of TXA in reducing intraoperative blood loss significantly during resection of PFTs in pediatrics. There was a mean reduction of blood loss of 138 ml with the use of TXA. The blood loss in terms of weight was found to be higher in Group B. Although this was not statistically significant possibly due to the small number of patients, it was clinically important. These findings are similar to previous studies in adult neurosurgical patients. In a trial evaluating the use of TXA in elective craniotomy for the excision of supratentorial tumors, Vel et al [9] found a significant reduction in intraoperative bleeding, yet without a corresponding decrease in the need for blood transfusions. Our study is novel, as there is limited literature on the use of TXA during PFT resection in the pediatric population.

Table 3
Summary of studies reporting efficacy of tranexamic acid in paediatric neurosurgical procedures

Study	Type of Study	Total number of patients/ Age	Dose of Tranexamic acid	Type of surgery	Key results		
					Blood loss	Blood and blood product transfusion	Other findings
Eustache et al [12], 2022	Retrospective study	102 infants, 3.5 to 12 months of age	Loading dose of 10 mg/kg over 15 minutes followed by 10 mg/kg/hr infusion until skin closure	Paediatric monosutural craniosynostosis surgery	The estimated blood volume lost (EBVlost) lower in the TXA group. EBVlost – 55.3 ml/kg in patients without TXA and 30.5 ml/kg & 25.7 ml/kg with TXA	Volume of blood transfusion reduced by > 50% with TXA, median volume of FFP transfusion reduced by 100% with TXA use	Reductions in postoperative drain output, total hospital length of stay
Goobie et al [14], 2020	RCT	68 children, 3 months to 2 year of age	High TXA (50 mg/kg followed by 5mg/kg/h) or low TXA (10 mg/ kg followed by 5 mg/kg/ h)	Paediatric craniosynostosis surgery	TXA 10 mg/ kg followed by 5 mg/kg/h not less effective than a higher dose of 50 mg/kg and 5 mg/kg/h in reducing the blood loss		
Kurnik et al [10], 2017	Retrospective study	114 patients, 15.4 ± 13 months (non-TXA group), 16.2 ± 14 months (TXA group) of age	10 mg/kg loading dose followed by a 5 mg/kg/h infusion for the first 24 hours	Open calvarial vault and anterior vaults	Weight-based EBL significantly lower in TXA (25 cc/kg in the TXA group vs 34 cc/kg in the non-TXA group [P.0.0143]	Less blood transfusion of 264 cc in TXA group versus 428 cc in non-TXA, P < 0.0001)	Pediatric intensive care unit length of stay shorter in TXA group, no significant difference in total hospital length of stay
Maugans et al [15], 2011	Retrospective study	56 patients	100-mg/kg bolus over 20 minutes followed by 10 mg/kg per hour	Minimally invasive craniosynostosis procedures	Median Estimated Blood Loss (EBL) significantly lower for TXA recipients compared with placebo (9.62 vs 15.94 mL/kg, P = 0.0231)	Transfusion incidences were 80% TXA versus 100% control (P = 0.4737)	No adverse events reported
				Open craniosynostosis procedures	Median EBL TXA recipients lower but not significantly different than for nonrecipients (21.86 vs 23.40 mL/kg, P = 0.7416)	Median transfusion volume for TXA recipients versus nonrecipients = 34.01 vs 40.35 mL/kg (P = 0.3137)	

RCT – Randomized controlled trial, TXA = tranexamic acid, EBV = estimated blood volume.

Study	Type of Study	Total number of patients/ Age	Dose of Tranexamic acid	Type of surgery	Key results		
					Blood loss	Blood and blood product transfusion	Other findings
Dadure et al [16], 2011	RCT	40 children, 3 to 15 months of age	15 mg/kg TXA during a 15-min period followed by continuous infusion of 10 mg/kg per hour until skin closure	Craniosynostosis surgery	The amount of intraoperative and total blood loss less in TXA compared with placebo (51.4 ± 28.3 vs. 61.1 ± 16.8 ml/kg and 64.0 ± 32.4 vs. 76.0 ± 16.1 ml/kg, respectively)	The volume of PRBC transfusion was significantly reduced by 85% during the intraoperative period and by 57% during the whole study period	There was no difference between groups for fluid therapy, hemodynamic monitoring, and urinary output.
Goobie et al [13], 2011	RCT	43 children, 2months to 6 year of age	loading dose of 50 mg/kg TXA as an infusion over 15 min, followed by an infusion of 5 mg/kg/h .	Craniosynostosis reconstruction surgery	The TXA group had significantly lower perioperative mean blood loss (65 vs. 119 ml/kg, P < 0.001) than placebo	Lower perioperative mean blood transfusion (33 vs. 56 ml/ kg, P < 0.006). TXA administration also significantly diminished (by two thirds) the perioperative exposure of patients to transfused blood (median, 1 unit vs. 3 units; P 0.001)	
Bharat et al [20], 2011	Letter of correspondence	1 child, 2-year-old	10mg/kg bolus	Highly vascular lateral ventricular choroid plexus carcinoma	TXA at 10mg/kg bolus given as a desperate measure to control bleeding and after 8 minutes, surgeon reported satisfactory hemostasis.		
Sethna et al [19], 2005	RCT	44 patients, 8– 18 year of age	100 mg/kg tranexamic acid before incision followed by an infusion of 10 mg /kg/ h	Scoliosis surgery	Blood loss reduced by 41% compared with placebo (1,230 ± 535 vs. 2,085 ± 1,188 ml; P < 0.01)	No difference between groups in amount of blood transfused (615 ± 460 vs. 940 ± 718 ml; P ± 0.08)	

RCT – Randomized controlled trial, TXA = tranexamic acid, EBV = estimated blood volume.

Study	Type of Study	Total number of patients/ Age	Dose of Tranexamic acid	Type of surgery	Key results		
					Blood loss	Blood and blood product transfusion	Other findings
Durán et al [17], 2003	RCT	20 patients,	15 mg/kg of intravenous TA upon anesthetic induction, every 4 hours during surgery, and every 8 hours throughout the 48 hours after surgery.	Pediatric cranial remodeling surgery	Less bleeding during surgery in TXA group than control (199 +/- 60 vs 290 +/- 43 mL)	Less need of intraoperative (176 +/- 104 vs 206 +/- 70 mL) and postoperative transfusion (9 +/- 28 vs 52 +/- 72 mL) 24 hours after surgery.	Less time in the recovery unit (60 +/- 14 vs 72 +/- 11 hours). Blood test variables in TA-treated children were also better 24 hours after surgery with regard to hemoglobin (12.1 +/- 2 vs 11.6 +/- 1.3 mg/dL) and platelet (261 +/- 68.5 vs 181.6 +/- 58.1 platelets/mm3) concentrations. There were no adverse events.
Neilipovitz et al [18], 2001	RCT	40 patients, 9– 18 year of age	Initial dose of 10 mg/kg followed by infusion of 1 mg/ kg/ h.	Scoliosis surgery	Intraoperative blood loss in the TXA group (2453 ± 1526 mL) not significantly different (P < 0.58) than in control group (2703 ± 1292 mL)	The total amount of blood transfused to the TXA group (1253 ± 884 mL) significantly less (P < 0.045) than the control group (1784 ± 733 mL)	
Present study	**Retrospective study**	**50 patients, 8 years (IQR, 2–17)**	**10–15 mg/kg over a period of 20 minutes before scalp incision, followed by a maintenance dose of 3–5 mg/kg/hr every three hours, until skin closure**	**Posterior fossa Tumour Excision**	**The mean estimated blood loss was 224.29 ± 110.36 ml in patients in patients who were administered TXA (n = 36) and 362 ± 180.11 ml in those who were not (n = 14), (p-= 0.007).**	**The requirement of blood and blood product transfusion was similar between the groups, but the volume of blood transfusion per kg body weight was higher in non-TXA group, 8.3 (IQR, 6.7–11.1) ml versus 10.5 (IQR, 8.1–16.1) ml in TXA group**	**The volume of crystalloid use intraoperatively was significantly higher in children who were not given TXA (p = 0.04). There were no adverse events.**

RCT – Randomized controlled trial, TXA = tranexamic acid, EBV = estimated blood volume.

The overall requirement of blood and blood product transfusion was found to be comparable between the two groups. There can be two explanations for the same. Firstly, the historical cohort of controls who did not receive TXA is small in number to achieve a statistically significant result. However, they were carefully matched for other characteristics. Secondly, in our institute blood transfusion is based on a definite protocol depending on the calculation of maximum allowable blood loss (MABL), point of care evaluation of Hb value,

coagulation profile and hemodynamic triggers. In our study, though the requirement of allogenic blood transfusion was not reduced with the use of the antifibrinolytic drug, the use of crystalloids was significantly less in Group A. Usually, the blood loss would be replaced by 3 ml of crystalloid solutions per millilitre of blood loss. A blood loss less than or equal to MABL with no significant ongoing or anticipated blood loss in the postoperative period does not warrant the use of packed red blood cells (PRBCs).[3] Pediatrics with adequate replacement of intravascular blood volume to prevent hypovolemia can tolerate anemia well and hematocrit can be maintained in the range of 20–25%. This was the rationale for the use of the higher volume of crystalloids to replace blood loss or for treatment of clinically indicated hypovolemia, in patients who were not administered TXA. Healthy pediatrics without coagulation deficits (pre-surgery) can be managed without using blood products until the blood loss equals their blood volume.[25] This could be the reason for the low requirement for blood products. The total mean volume of blood transfused and in terms of body weight was found to be less with TXA administration (Table 2). This was not statistically significant but can be considered clinically important. A prospective study conducted by Hooda et al[5] on the effect of TXA on blood loss during intracranial meningioma excision in adult patients also demonstrated similar findings in the form of intraoperative bleeding reduction by 27% (RR 1.3 [1.1–1.8], p = 0.03), and a tendency to reduce the number of blood transfusions, but without statistical significance (P = 0.89) [8]. A retrospective cohort study performed with 519 adults (245 of whom received TXA) who had undergone a complex neurosurgical procedure for skull base tumors showed significantly lower transfusion rates (P = 0.04) in the TXA-treated group (13% versus 7% in the control group) [7]

TXA related side-effects

No patient who received TXA in our patient cohort had any adverse event like a seizure, thromboembolic episodes or acute kidney injury, that have been reported previously in the literature [26]. Our protocol for TXA administration is thus safe and beneficial during the excision of PFTs in pediatrics. The safety has also been established in pediatric patients undergoing cardiac procedures [24].

The thromboembolic events in the pediatric population are uncommon and in our study as well, the use of TXA was not associated with an increased risk of venous thromboembolism. Mebel et al [7] in their retrospective study also concluded that the use of TXA is safe, with no significant differences in the rate of thromboembolic events as compared with the control group.

There are some limitations to our study. This is a retrospective observational study and the administration of TXA was not randomized. There can be a variability in the dose of TXA administered. Only the requirement of blood and blood products transfusion was noted and the exact volume of blood given was not recorded. The patients operated in a single unit, operated by a single surgeon were included to remove the confounding factors related to surgical techniques. Despite the retrospective nature of our study and the small number of historical controls, we have demonstrated the safety and efficacy of TXA in pediatrics undergoing excision of PFTs with respect to a significant reduction in intraoperative blood loss. Prospective studies that evaluate different dose regimens of TXA in this population may be planned in future to validate our findings

TXA is safe and efficacious in reducing blood loss in pediatrics undergoing resection of posterior fossa tumors. Our findings provide a basis for future randomized trials to determine the optimal dose regime of TXA in this patient population.

Abbreviations

PFT: posterior fossa tumors, TXA : tranexamic acid, MABL : maximum allowable blood loss**,** PRBC: packed red blood cells.

Declarations

Ethics approval and consent to participate: Yes, Institutional Ethics Committee approval (IRB: 11456) obtained.

Consent for publication: Not applicable

Availability of data and material: yes

Competing interests : Not applicable

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Authors' contributions: Author 1 and 2: This author helped with conception and design, acquisition of data, interpretation of data and drafting the article, Author 5: This author helped with conception and design, analysis and interpretation of data, drafting the article or

revising it critically for important intellectual content; Agree to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Author 3, 4 : These authors helped with conception and design, drafting the article, proofreading or revising it critically for important intellectual content. All authors approved the final version to be published.

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Figures

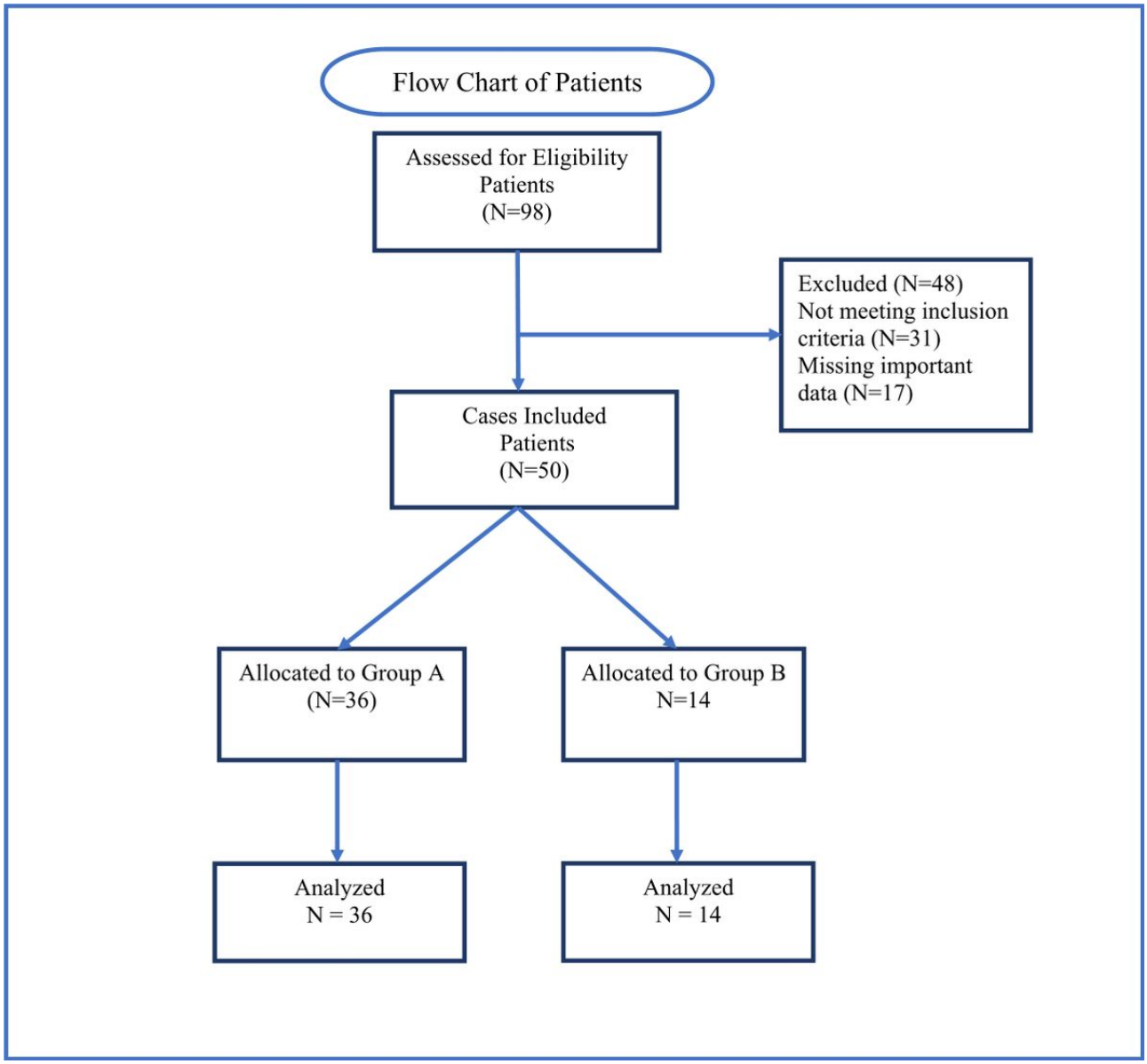

Figure 1

Diagram showing the flow of participants through the study.