Official Title of the Study:

A Prospective Randomized Clinical Trial to Evaluate the Impact of Intraoperative Ventilation with High Oxygen Content on the Extent of Postoperative Pneumocephalus in Patients Undergoing Craniotomies

NCT number: NCT02722928

Last approved continuing review on: 08MAR2018

IRB protocol number: 2015H0032

- Initial submission approved on: 27JAN2015
- IRB confirmed closure date: 26DEC2018

Objectives

Primary Objective

We compared the rate of occurrence and volume of postoperative pneumocephalus in patients undergoing craniotomies (hemispheric or posterior cranial fossa tumors and microvascular decompression) and receiving intraoperative ventilation with pure oxygen versus a conventional air/oxygen 1:1 mixture during the last stage of surgery (hemostasis and wound closure)

Secondary Objectives

We compared the incidence and volume of postoperative pneumocephalus in patients undergoing surgery in sitting and supine positions. Furthermore, we compared postoperative neurological outcomes and intensive care unit length of stay among neurosurgical patients (posterior cranial fossa tumors, supratentorial tumors, and transsphenoidal /endoscopic procedures)

Study Design

We conducted a prospective randomized single-blinded study at The Ohio State University Wexner Medical Center enrolling patients (≥ 18 years) with an American Society of Anesthesiologists (ASA) physical status of II–IV undergoing neurosurgeries (supra- and infratentorial tumors such as astrocytomas and glioblastoma multiforme, and microvascular decompression) in sitting, prone, lateral, park bench, and other positions.

Sample Size and Statistical Analysis

We estimated that a sample size of 80 patients per group would confer a greater than 80% power to detect a 20% decrease in volume in the intervention group with an alpha of 0.05 considering a mean pnemocephalus volume of 87 ml in the control group (standard deviation of 40). The sample size was estimated based on published data. Our proposed intervention is considered harmless, being applied routinely in perioperative settings. No intervention-related adverse events were expected during the study.

Categorical variables were reported as frequencies and percentages and compared between randomization groups using Chi-square tests or Fisher's exact tests where relevant. Continuous variables were reported as means and standard deviations or medians and interquartile ranges and compared between randomization groups using Student's t-tests or Wilcoxon rank sum tests where relevant. Hypothesis testing was conducted at a 5% type 1 error rate (alpha=0.05). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Randomization

The study was planned and conducted according to all the required institutional and state regulations related to clinical research. Patients were randomly distributed (random table) into two groups:

- Control Group (A): received controlled ventilation throughout the surgery with a conventional air/oxygen 1:1 gas mixture (FiO_2 60%)

- Interventional Group (B): received controlled ventilation with a conventional air/oxygen 1:1 gas mixture from the beginning of the surgery and during the tumor removal phase. However, patients in group B were switched to controlled ventilation with

100% O_2 once the tumor resection was completed and hemostasis started until extubation

Study Procedures

Both groups received supplemental oxygen via nasal cannula as a standard of care during the early postoperative period. A standard CT scan was performed within 6 hours post-surgery for both groups. CT scans were assessed and interpreted by a blinded radiologist in order to diagnose the frequency and the extent of postoperative pneumocephalus (quantification). TeraRecon Intuition software version 4.4.11.265.8092 was used, retrieving the CT scan data from the system and loading it into the software program. All CT data maintained a 1 mm slice increment. The air in the skull was identified and circled using a region of interest (ROI) tool. The area defined for measurements applied in this study was within the skull in any space occupied by brain. This excluded any air trapped between the bone from graft placement or between the skin and the skull. Once all the visually identified areas of "air" were circled and then selected within the skull, a Hounsfield unit (HU) threshold tool was used to remove any excluded tissue. The setting of -150 HU or less was applied, and the selected areas were presented in 2D and 3D. Only the areas identified within the ROI accounted for the 3D image. The volume was calculated in cm^3 using the software presented by clicking the "volume" measurement tool. Considering similarity of the groups and randomization, it was expected that the duration of the last part of surgery and the lapsing time from the end of surgery to postoperative CT acquisition to be the same for the control and treatment groups. The following data was considered for intergroup analysis and selection bias exclusion: demographics (age, gender, weight, and body mass index), oxygen inhalation time, the period of time elapsed from the end of surgery to CT scan completion. The occurrence of adverse events and neurological status were assessed before the CT scan and compared with the baseline evaluation. Stage 1 was defined as the interval of time (minutes) measured from skin incision to the onset of hemostasis (i.e. after tumor removal). Stage 2 was defined as the interval of time (minutes) measured from the onset of hemostasis to incision closure. We conducted study intervention (for group B) during stage 2.

DISCUSSION

Our prospective randomize study is the first to examine the prophylactic effect of normobaric hyperoxygenation on limiting the extension of postoperative pnuemocephalus volume in patients undergoing elective neurosurgery. A total of 70 patients were included into our final analysis. The study showed no pneumocephalus volume reduction when higher oxygen concentration (FiO2 100% vs 60%) was used prophylactically during the last stage of surgery in patients undergoing craniotomy ($p= 0.47$). We estimated that our intervention would produce a 20% decrease in pneumocephalus volume for the interventional group. However, after enrolling 105 ($N=105$) patients, an unanticipated blinded analysis showed that the variability relative to the pneumocephalus volume mean was much higher than initially assumed based on published data. Therefore, we determined that our study was underpowered and an unfeasible number of patients would have been required ($N>400$ patients/group) to be enrolled in order to detect the expected difference between groups.

Figure 1. CONSORT Flow Diagram

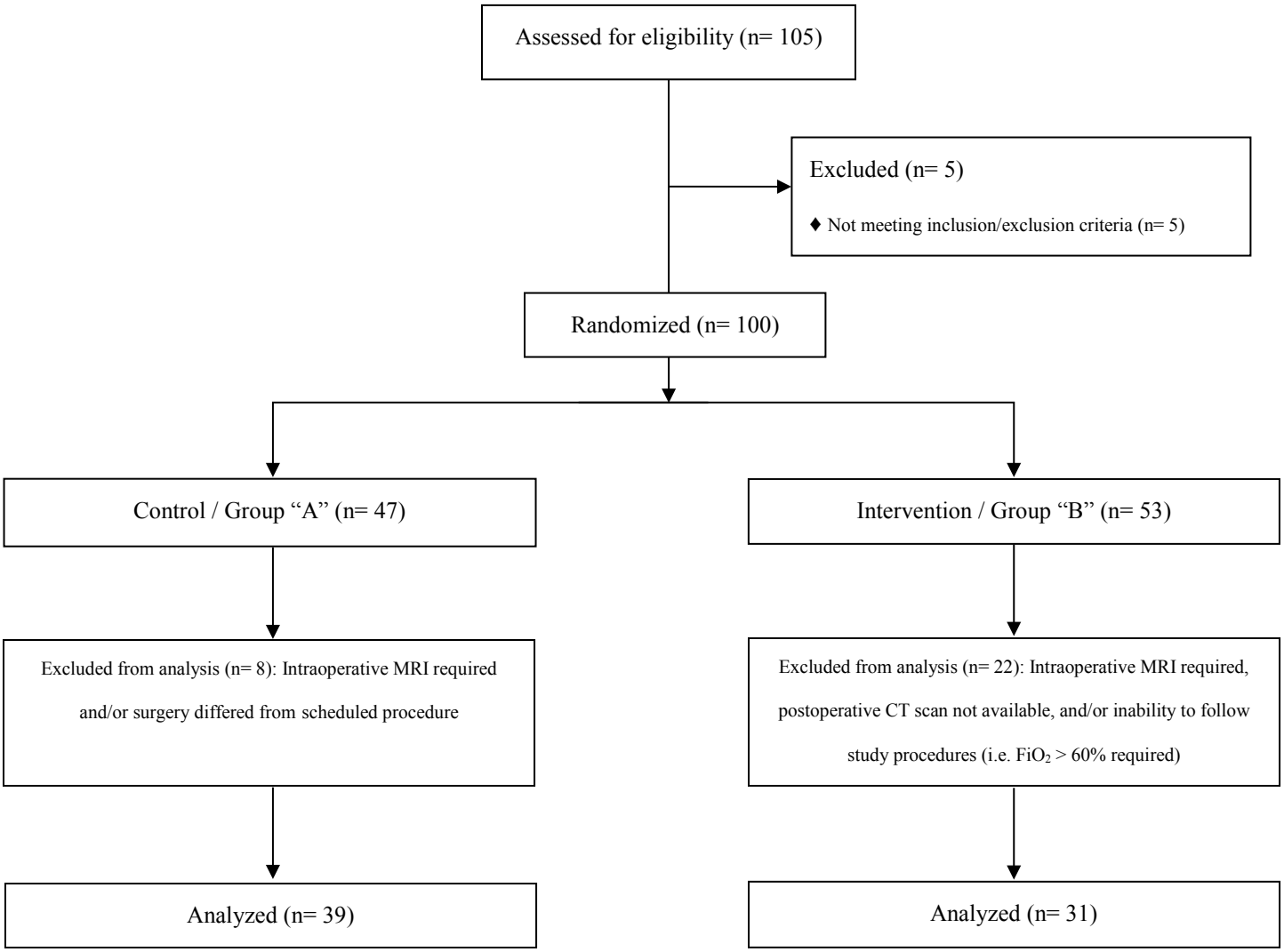

Table 1. *Demographic and Clinical Variables*

Variable	Control n= 39	Intervention n= 31	*p* value
Age *(mean ± SD)*	46.69 (14.21)	50.81 (13.28)	0.2198
Gender *n (%)*			
• Female	23 (58.97)	14 (45.16)	0.2501
• Male	16 (41.03)	17 (54.84)	
Race *n (%)*			
• White	36 (92.31)	27 (87.10)	0.6916
• African-American	3 (7.69)	4 (12.90)	
Biometrics *mean ± SD*			
• Weight *(Kg ± SD)*	89.00 (21.69)	94.00 (17.67)	0.3034
• Height *(cm ± SD)*	168.31 (10.29)	172.30 (10.90)	0.1208
• BMI *(Kg/m^2 ± SD)*	31.35 (7.42)	31.94 (6.64)	0.7301
ASA *n (%)*			
• I	0 (0.00)	1 (3.23)	0.8874
• II	12 (30.77)	9 (29.03)	
• III	26 (66.67)	20 (64.52)	
• IV	1 (2.56)	1 (3.23)	
Preoperative Diagnosis *n (%)*			
• Supratentorial lesion	25 (64.10)	21 (67.74)	0.7500
• Infratentorial lesion	14 (35.90)	10 (32.26)	

n= number of patients; ASA= American Society of Anesthesiologists

Table 2. *Perioperative Variables*

Variable	Control n= 39	Intervention n= 31	*p* value
Surgical Positioning *n (%)*			
Sitting	1 (2.56)	0 (0.00)	
Semi-sitting	0 (0.00)	0 (0.00)	
Prone	10 (25.64)	3 (9.68)	0.1233
Lateral	7 (17.95)	11 (35.48)	
Park bench	0 (0.00)	0 (0.00)	
Supine	21 (53.85)	17 (54.84)	
Procedure Performed *n (%)*			
Conventional Anterior Fossa	23 (58.97)	16 (51.61)	
Conventional Posterior Fossa	15 (38.46)	11 (35.48)	
Conventional Middle Fossa	0 (0.00)	3 (9.68)	0.1535
Minimally Invasive Anterior Fossa	0 (0.00)	1 (3.23)	
Minimally Invasive Middle	1 (2.56)	0 (0.00)	
Ventilatory parameters *beginning of stage 2 [median and IQR]*			
Ppeak *(cm H_2O)*	21.0 [19.0 – 25.0]	22.0 [20.0 – 25.0]	0.3734
PEEP *(cm H_2O)*	4.9 [4.0 – 5.0]	5.1 [4.4 – 7.0]	0.0215
$EtCO_2$ *(mm Hg)*	29.0 [28.0 – 32.0]	30.00 [28.0 – 32.0]	0.8726
Length of stage 1 *[median and IQR]*	177.0 [140.0 – 223.0]	256.0 [145.0 – 344.0]	0.0596
Length of stage 2 *[median and IQR]*	49.0 [34.00 – 63.0]	55.0 [39.0 – 68.0]	0.3688
Postoperative Recovery Location			
PACU	6 (15.38)	3 (9.68)	0.7214
SICU	33 (84.62)	28 (90.32)	
Length of PACU stay *(min ± SD)*	344.67 (455.51)	178.33 (147.60)	0.5683
Length of SICU stay *(min ± SD)*	1,380.0 [1,112.0 – 2,096.0]	1,524.5 [1,312.0 – 2,814.5]	0.1880
End of Surgery - CT scan interval time in minutes *[median and IQR]*	89.0 [61.0 – 125.0]	80.0 [62.0 – 127.0]	0.8229
Postoperative pneumocephalus in cm^3 *[median and IQR]*	9.65 [3.61 – 23.20]	7.06 [2.70 – 20.1]	0.4768

n= number of patients; Ppeak= peak inspiratory pressure; PEEP= positive end-expiratory pressure; $EtCO_2$= end- tidal CO_2; PACU= post-anesthesia care unit; SICU= surgical intensive care unit; CT= computed tomography

Table 3. *Postoperative Pneumocephalus Volume in cm^3 [median and IQR] according to Procedure Performed*

Conventional Anterior Fossa	**Control** n= 23	**Intervention** n= 16	***p* value**
	17.40 [6.89 – 24.40]	13.95 [4.82 – 22.15]	0.4797
Conventional Posterior Fossa	**Control** n= 15	**Intervention** n= 11	***p* value**
	4.38 [0.81 – 10.50]	4.00 [0.60 – 13.00]	0.8775

Table 4. *SICU LOS according to Procedure Performed (median min [IQR])*.

Conventional Anterior Fossa	**Control** n= 23	**Intervention** n= 16	***p* value**
	1380 [1112.0 – 1665.0]	1489.0 [1337.0 – 2814.5]	0.2017
Conventional Posterior Fossa	**Control** n= 9	**Intervention** n= 9	***p* value**
	2059.0 [1102.0 – 3049.0]	1342.0 [1203.0 – 1665]	0.7943

SICU= surgical intensive care unit; LOS= length of stay

Table 5. Changes in Neurological Outcomes at POD 3 Compared to Preoperative Evaluation

Neurological Outcome Variation *n (%)*	**Control** n= 39	**Intervention** n= 31	***p* value**
Improvement	8 (20.5)	6 (19.3)	
No changes	25 (64.1)	15 (48.4)	0.23
Deterioration	6 (15.4)	10 (32.3)	

POD= postoperative day; n= number of patients