Protocol for Sedatives' Effects on Neurological Function in Patients With Eloquent Area Glioma
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Background

Sedation in the operating room, the Post Anesthesia Care Unit, and the Intensive Care Unit (PACU) is common and often necessary for patients with intracranial brain tumors. Repeated neurological function assessments are needed, especially in patients with tumors in or near eloquent regions. This is to monitor neurologic performance to determine if there are alterations that require treatment[1]. Some slowly infiltrative low-grade gliomas near eloquent regions do not show any clinically detectable neurologic deficits, perhaps from neuronal reorganization[2,3]. However, with sedation by some GABAergic sedatives the disease may manifest or seem much worse resulting in inappropriately aggressive treatment[4]. This may be especially problematic in patients undergoing awaked craniotomy for tumors in eloquent regions.

Midazolam sedation has been found to profoundly exacerbated or unmask motor deficits in patients with supratentorial mass lesions, and these deficits primarily involved limb motor function or ataxia according to our previous study using National Institutes of Health Stroke Scale (NIHSS) evaluation[5], and neither the mechanism nor the reversibility of effects will be investigated in that study. However, limb ataxia will be shown the worst reliability in stroke a patient under NIHSS, in a modified NIHSS, limb ataxia will be removed with other 3 items (consciousness, facial palsy, dysarthria) [6,7]. For patients with brain tumor with positive change in limb ataxia, it is hard to conclude an unreliable false positive or truly impaired ataxia that may indicate the disrupted motor-sensory function integrity. Nine-hole peg test has good reliability to test upper limb dexterity and motor co-ordination, hand/eye co-ordination as well as ability to follow simple directions[8,9], it can be applied to test midazolam induced motor deficits effects and reversibility.

This will be a single-center prospective non-randomized study. Patients will be mildly sedated to keep them responsive and cooperative. Motor and sensory function will be evaluated before and after mild sedation as well as after midazolam reversal by the specific benzodiazepine antagonist flumazenil. 9-hole peg test will be used to test the motor-sensory function because it requires motor coordination, accurate reading and sensorimotor integration.

The aim of the study is to (1) determine whether the neuronal deficits are mediated specifically through benzodiazepine sites by demonstrating reversibility with flumazenil; (2) more precisely document the midazolam induced motor-sensory

function and coordination worsening; (3) investigate how specific patient populations with eloquent areas gliomas react to mild midazolam sedation.

We hypothesized that mild sedation by midazolam can unmask or exacerbate upper limb's motor and sensory deficits in patients with eloquent area gliomas but not in non-neurosurgical patients; the neurologic deficits induced by midazolam can be reversed by antagonist flumazenil.

Materials and Methods

Study Design

This will be an interventional, parallel assignment, interventional non-randomized trial and will be approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (approval number: KY2014-040-03). This study was registered in ClinicalTrials.gov (registration No. is NCT02439164).

Population

Elective neurosurgery patients with supratentorial eloquent area gliomas diagnosed by Magnetic Resonance Imaging (MRI) will be eligible for this study.

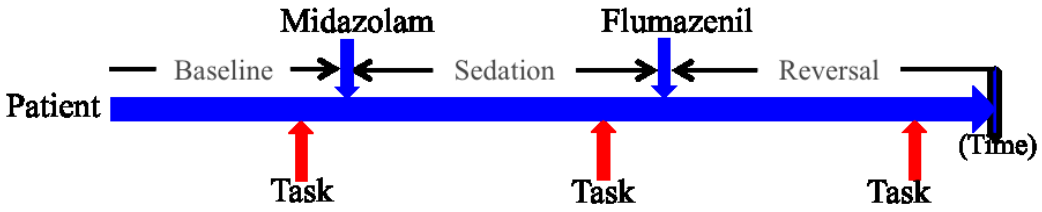
Inclusion Criteria and Exclusion Criteria

The inclusion criteria will be the age between 18 and 60 with American Society of Anesthesiology (ASA) status I~II. The control group enrolled volunteers in the same age but without neuro-diseases. The exclusion criteria will be based on the hospital record documentation screening: unable to comprehend and cooperate with the neurologic examination, impaired mental status, taking sedative drugs by any way in the past 24 hours, taking any type of pain reliever by any way in the past 24 hours, drug and/or alcohol abuse, pregnant and/or lactating women, recurrent glioma, multiple brain glioma, accepting radiotherapy or chemotherapy, complicated with intracranial trauma and vascular diseases, complicated with grand mal epilepsy, complicated with neuromuscular diseases and complicated with cutaneous paresthesia.

Study interventions

Patients' demographic characteristics, clinical manifestations and past history will be obtained before the study. On the day of study, subjects will be admitted into the operating room in supine position with the head up at 60 degree. Nasal cannula will be used for providing oxygen. Vital signs including blood pressure (BP), heart rate (HR), pulse oxygen saturation (SpO_2) will be monitored and recorded before and after the treatment. Observer's Assessment of Alertness and Sedation (OAA/S) will be evaluated and recorded before and after drugs administration, OAA/S is from 1 to

5 indicating deep sleep to fully alert (5 = alert, 4 = lethargic, 3 = aroused by voice, 2 = aroused by shaking, 1 = deep sleep). Nine-Hole Peg Test (Rolyan® A851-5, United Kingdom) will be used to evaluate motor function after midazolam sedation and flumazenil reversal in each hand. After obtaining the baseline vital signs and 9-Hole Peg Test data, small dose of midazolam from 0.02mg/kg as initial dose will be given intravenously to get OAA/S=4 which will be arousalble and fully cooperative sedation, if the sedation level will be not reached, additional titration dose of 0.01mg/kg will be given, waited for 3-5 minutes to allow reaching peak effect after each administration and ensured OAA/S =4 as well as fully cooperative, 9-Hope Peg Test will be then repeated. After the evaluation, specific benzodiazepine receptor antagonist flumazenil at 4μ/kg will be given intravenously to reverse midazolam's sedation till OAA/S=5, 9-Hole Peg Test will be then repeated again to test the motor function as shown below. Other drugs (e.g. atropine for bradycardia) prescribed as needed, will be also recorded. Detailed descriptions of the lesion in MRI will be obtained. The lesions' pathologic diagnoses will be obtained two weeks after the tumor removal.



The interventions will be stopped if any of the following occurs: systolic blood pressure less than 90mmHg or more than 180mmHg after the drugs, heart rate less than 50bpm after 0.5mg atropine, SpO2 less than 90%, over sedated as indicated by OAA/S equal or less than 3, any of the drug related side effect occurred such as respiratory depression, unstable hemodynamic, agitation etc.

Nine-Hole Peg Test[9] will be the major task for upper extremities evaluation in this study. It is to test motor coordination, eye/hand coordination and the ability to follow simple directions, and it requires brain sensorimotor integration. The testing board is a square board with 9 holes that are spaced 1.25 inches apart in a 3×3 array, each hole is 0.5 inches deep; each peg is 1.25 inches long and 0.25 inches in diameter. The pegboard will be centered in front of the subjects with the container holding the pegs placed on the hand being tested. The instruction will be provided while the demonstration will be shown. Subjects will be instructed to pick up the pegs one at a time using testing hand and put them into the holes in any order as quickly as they can until all the holes will be filled, and then remove the pegs one at a time and return them to the container in the full speed, the un-testing hand will be

used to stabilize the peg board. After the subjects performed the practice trials, they will be instructed the actual test as before. The outcome measure will be the length of time from the first peg subject touches to the last peg hits the container. The ipsilesional hand will be firstly tested in glioma patients group and dominant hand will be firstly tested in normal control group; after the first testing, the container will be placed on the opposite side of the pegboard and repeated the testing with the contralesional hand in glioma group and with non-dominant hand in control group. Timing will be performed with a stopwatch and recorded in seconds by a same nurse during whole study period. Patients and the doctors who administered drug will be blinded of the timing. This test will be firstly performed before the administration of medication at baseline, as well as after midazolam and flumazenil administered to each patient.

The primary outcomes will be the changes of task performing time after midazolam sedation and flumazenil reversal compared to the normal control.

The secondary outcomes will be the differences of performing time among baseline, midazolam sedation and flumazenil reversal; as well as the differences of time changes between two types of gliomas.

Sample size justification

Based on a previous study, with an estimated standard deviation of 10.0 and with a significance level (alpha) of 0.05 using a two-sided one-sample t-test. The minimum number of cases will be 15 in one group achieves 95% power to detect a possible statistical difference between any of two groups. Allowing 20% rate of drop-out, we raised the case number to 18 for each group, as 1:1 assignment in experimental group and control group, we aimed to enroll at least 36 subjects in total. Sample size will be calculated by PASS11.0.2 (Copyright © 1983-2011. NCSS Statistical Software, Kaysville, Utah)

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