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Title: Effect of single dose of tramadol on extubation response and quality of emergence following supratentorial intracranial surgery

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Study Protocol:

Extubation after intracranial tumor surgery is desirable in order to make an early diagnosis of intracranial complications. Extubation however, may be associated with hemodynamic and metabolic changes e.g. agitation, increased oxygen consumption, catecholamine secretion, hypercapnia and systemic hypertension (1). These changes cause cerebral hyperemia, intracranial hypertension leading to cerebral oedema or haemorrhage, thus it is important to have smooth extubation with minimal haemodyamic and metabolic effects.

Incidence of coughing on emergence from general anesthesia ranges from 38% to 96%(2) This may also result in postoperative intracranial hemorrhage, intracranial hypertension, cerebral edema or intraocular hypertension (2). This can be detrimental in neurosurgery.

Several modalities have been studied to prevent coughing during emergence, including extubation in a deep plane of anesthesia (3, 4) but have proved to be unreliable. So far, no reliable method is recommended as standard of care.

Tramadol, a synthetic opioid of the aminocyclohexanol group, is a centrally acting opioid analgesic that is used to treat moderate-to-severe pain and has an inhibitory effect on M1 and M3 muscarinic receptors. It also reduces the incidence of cough and improves extubation quality, and provides more stable hemodynamics during emergence (2). It neither causes respiratory depression, nor affects intracranial pressure (ICP) and cerebral perfusion pressure (CPP) (5). Other potential advantage of administering tramadol includes a long duration of action, rapid recovery, limited depression of respiratory function (6) and no effect on platelets (7) thus making it a safe medication to use for neurosurgical patients after craniotomy. The onset of effect following a single dose is 3 to 5 minutes with peak effect at 45 minutes (8).

Aim of doing this study is to observe the effect of a single dose of tramadol on quality of tracheal extubation as judged by incidence of coughing and hemodynamic changes at emergence from anesthesia.

Methodology:

This double-blind randomized controlled trial will be conducted over a period of two years, 2016 and 2017. A total of 80 patients will be recruited in the study after permission from the Ethics Review Committee of hospital. Power calculation will be based on hemodynamic response. Thirty-four subjects in each group will be recruited to achieve 80% power to detect an absolute difference i.e. 10 mmHg and standard deviation of 10-15 mmHg with 5% type I error. We plan to recruit 80 patients, to account for a 15% dropout rate. Sample size estimation is based on a previous study (3).
Patients will be recruited in the study during the preoperative anesthesia evaluation either at the preoperative clinic or after admission to the ward. After taking informed written consent, each medical record number will be sent to the Clinical Trials Unit (CTU), along with their expected date, day and timing of surgery. The CTU will randomly allocate the patients to one of the two groups, based on computer-generated allocation. After the

patient will reach the preoperative area in the operating room (OR) an e-mail request will be generated to the CTU who would release the prepared study drug syringe and will send it to the principal investigator (PI). The syringe will contain either tramadol (volume 10mg/ml in a 10 ml syringe) or placebo 0.9% normal saline in the same volume. Drugs for both groups will look alike so that patient, investigator, anesthetist administering the drugs or those making observations are all be blinded.

Intraoperatively anesthesia care will be standardized. After application of electrocardiography (ECG), non-invasive blood pressure (NIBP) monitor and pulse oximeter, baseline heart rate (HR), invasive blood pressure (BP) and oxygen saturation (SpO2) will be recorded. Preoxygenation will be done for 3minutes with oxygen administered at a rate of 5 l/min via a breathing circuit. Anesthesia induction will be done with propofol (2 mg/kg) intravenously (IV) and fentanyl (2 μg/kg) IV followed by atracurium (0.6mg/kg) IV. Maintenance of anesthesia will be achieved with oxygen (O2), nitrous oxide (N2O) in 1:2 ratio, isoflurane (0.8–1%) and atracurium infusion (0.4 mg/kg/hr-). Ventilation will be set at 8 ml/kg, volume controlled mode and respiratory rate adjusted to achieve a level of end-tidal carbon dioxide (ETCO2) of 29–30 mmHg. An arterial line will be inserted in radial artery for continuous invasive blood pressure monitoring, ECG, SpO2, capnography, inspiratory and expiratory concentrations of isoflurane minimum alveolar concentration (MAC) and N2O percentage, as well as neuromuscular block, will continuously be monitored. Paracetamol 1 gram will be infused over 20 min in all patients after induction. Top up fentanyl 20 μg boluses will be administered if either the patient's HR or BP increased to 20 % above baseline and when other causes of tachycardia and hypertension are excluded. Atracurium infusion will be stopped 20 min before the end of surgery. Injection metoclopramide 10mg will be given in all patients at the time of closure of dura.

Study drug (tramadol 1mg/kg or normal saline bolus) will be administered to the patients by the anesthetist 45 min before extubation i.e. approximately at the time of dural closure. Reversal of residual muscle relaxation will be achieved with neostigmine (0.05mg/kg) and glycopyrrolate (0.01mg/kg) intravenously and time will be noted when the patient will start breathing spontaneously. Patients will be extubated after resumption of adequate spontaneous breathing, following verbal commands and with stable vital signs.

BP and HR will be recorded continuously from the arterial line, at 1 min before administration of reversal drugs till 5 minutes after extubation, then intermittently at 10 min interval for 30 min. Readings at 1, 2, 4 and 6 hours will be recorded postoperatively using noninvasive methods (CARESCAPE Monitor B650, GE Healthcare Ltd, Finland). Intravenous metoprolol 1mg bolus will be administered when hemodynamic values of BP and HR rose more than 20% from baseline values.

Cough will be recorded as either "yes" or "no" at the following time points: resumption of spontaneous breathing, when patients were able to respond to verbal commands, at the time of cuff deflation, at extubation and 2 min after extubation. Quality of tracheal extubation will be evaluated using a modified 5-point rating scale at the above-mentioned intervals, (5 = no coughing or straining; 4 = very smooth or minimal coughing; 3 = moderate coughing; 2 = marked coughing or straining; and 1 = poor extubation). [3] Any episode of bronchospasm, laryngospasm, or desaturation (oxygen saturation<92%) will also be noted during emergence and till 6 hours postoperatively. Sedation, PONV,

any episode of convulsions and drop in GCS will also be noted at 2, 4 and 6 h postoperatively as secondary outcomes of quality of emergence. The study will end at 6 hours post-extubation.
Pain will be assessed for 6 h postoperatively using verbal rating scale (VRS) with 0 = no pain and 10 = worst pain. Sedation will be assessed as 0=no sedation, 1= mild sedation (eye-opening on verbal commands), 2= moderate sedation (eye-opening on painful stimulus), 3= deep sedation (not waking up on pain). All patients will be prescribed paracetamol one gram IV six hourly and tramadol 50mg IV as rescue analgesia in the first 6 hours post operatively. Anti- emetic prophylaxis will be given with each dose of tramadol.

Statistical Analysis Plan:

Statistical analysis will be performed using Statistical Packages for Social Science version 19 (SPSS Inc., Chicago, IL). Quantitative point estimate will be presented as mean and standard deviation and analysis by independent sample t-test and Mann-Whitney U test after normality testing by Kolmogorov Smirnov test. Qualitative point estimates will be reported in term of frequency and percentage and analyzed by the chi-square test or fisher exact test. Repeated measure ANOVA will be applied to compare mean, SBP, DBP and HR between groups (within/between subject effect). $P \leq 0.05$ will be considered significant.
Data will be saved at primary investigator. Investigator will permit trial-related monitoring, audits and regulatory inspection by providing direct access to data. Decoding of the drugs will be done once the study is completed

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