

## Role of flupirtine in reducing preoperative anxiety of patients undergoing craniotomy procedure

### ABSTRACT

**Background:** Kv7 neuronal channels are recognized as a potential drug target for anxiolytic effects. We hypothesize that flupirtine as a potassium channel opener would effectively reduce the preoperative anxiety of patients undergoing craniotomy procedure.

**Methods:** In prospective-double-blinded fashion, 124 counseled patients were randomized to receive 5 sequential doses of capsule flupirtine 100 mg (F Group) or physically similar starch capsules (C Group), at 12 h intervals during preoperative hospitalization. Primary outcome included various aspects of patient anxiety measured by visual analog scale (VAS) just before preoperative counseling and 2 h after the completion of drug regimen under trial. Statistical tool included Mann–Whitney U-test and Wilcoxon signed rank test.

**Results:** Baseline VAS scores were higher for fear of surgical harm, being at the mercy of medical staff, and not awakening after surgery. A significant decline in VAS scores was observed after the completion of drug regime, but to a higher extent in flupirtine-treated patients; it achieved statistical significance in comparison to Group C. No side effects were observed in any patient.

**Conclusion:** Flupirtine is a useful premedication in conjunction with behavioral therapy to alleviate patient anxiety during the preoperative period.

**Key words:** Anxiety; craniotomy; flupirtine; visual analog score

### Introduction

Preoperative anxiety is an unpleasant emotion which affects the perioperative outcome of patients awaiting elective surgery. Its global incidence varies from 60% to 92% among different surgical groups.<sup>[1,2]</sup> Although an under-recognized phenomenon, it can have diverse consequences such as difficult venous access, delayed jaw relaxation, coughing during anesthetic induction, autonomic fluctuation, altered intraoperative hemodynamics and anesthetic requirements, higher postoperative pain, delayed recovery, and longer hospital stay.<sup>[3]</sup>

The traditional approach to reduce preoperative anxiety includes pharmacological anxiolysis with benzodiazepines, barbiturates, etc., or behavioral interventions such as patient counseling, distraction, attention focusing, and relaxation procedures. Although such therapies are helpful, their routine usage is limited by associated side effects or lack of desired intellectual level and illiteracy among patients.

Neuronal Kv7 channels have been recognized as a potential drug target for anxiolytic activity.<sup>[4]</sup> Flupirtine, a centrally

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acting analgesic known to possess N-methyl-d-aspartate antagonism, stimulates Kv7 neuronal channels. Additional benefits include preservation of respiratory functions, better gastrointestinal tolerability, preemptive analgesic effects, and antiepileptic properties.<sup>[5]</sup> Previous trials have observed its anxiolytic activity in an animal model; however, such end-point has not been investigated in a human trial.<sup>[6]</sup> We hypothesize that flupirtine would effectively reduce the preoperative anxiety of patients undergoing craniotomy procedure.

## Methods

After institutional ethical approval and written informed consent, all conscious, cooperative and oriented, brain tumor patients, aged 18–50 years of either sex, American Society of Anaesthesiologists (ASA) physical Status I–II, scheduled for elective craniotomy, in between August 2013 and July 2014, were included in this prospective, randomized, double-blinded, placebo-controlled trial. Patients with a history of psychiatric disease, end organ dysfunction, pregnancy, on antihypertensive, sedative, hypnotic, anxiolytic, analgesic or antidepressant medications, and history of drug allergy, were excluded from this study.

All patients were randomly assigned (using computer generated random numbers and sequentially sealed opaque envelope technique) to two groups: to receive capsule flupirtine 100 mg (F Group) or physically similar starch capsules (C Group) with a sip of water just after preoperative counseling (60 h prior to surgery) and four subsequent doses, 12 h apart during preoperative period [Figure 1].

Enrolled patients were directed to state their anxiety level in terms of visual analog scale (VAS) score on a 12-point questionnaire, at two time points: Just before preoperative counseling (baseline), and 2 h after the last dose of studied drug on the evening before surgery (second time point) [Figure 1]. All patients received a questionnaire for assessing anxiety which included 12 items (2: Assessed overall fear of anesthesia or surgery; 10: Assessed various

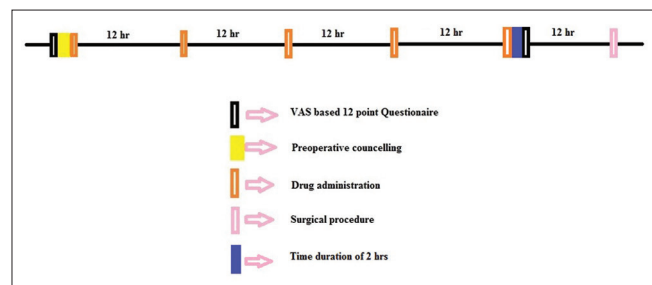


Figure 1: Time-points for performing various interventions

factors contributing to preoperative anxiety).<sup>[7]</sup> VAS score was based on 100-mm scale; extreme left indicate “no anxiety” while right end signify “maximal anxiety.” Various patient characteristics affecting preoperative anxiety were also noted and compared between the groups. Data were collected by an investigator blinded to group allocation.

Assuming that flupirtine would further decrease the VAS score by 20%, with a standard deviation of 25% estimated from initial pilot observations, 80% power and 5% alpha error, we required 26 patients in each group. The sample size was calculated using power and sample size calculator (Department of Biostatistics, Vanderbilt University, USA). Statistical analysis was performed by IBM SPSS statistics for windows, Version 17.0, (IBM Corp, Armonk, NY). The unpaired variables were compared by Mann–Whitney U-test. The paired variables were compared by Wilcoxon signed rank test. Discrete variables were compared by Fisher’s exact test/Chi-square test, whichever appropriate. The difference of  $P < 0.05$  was considered statistically significant.

## Results

The admission rate for elective craniotomy in our hospital is about 15–20/month. All such patients admitted during the study were screened for eligibility, with the target to include at least 26 patients per group. Out of 154 patients screened for our study during the study, 124 patients meeting the inclusion and exclusion criteria were randomized into two study groups and all of them completed the study successfully [Figure 2].

Baseline demographics, ASA physical status, use of anticonvulsants, educational status, information seeking behavior, and exposure to previous anesthesia were comparable between the groups. Among the various factors responsible for preoperative anxiety, VAS scores were higher for fear of surgery, of being at the mercy of medical staff, harm from anesthesia or surgery, fear about surgical outcome, and not awakening after anesthesia [Table 1]. Baseline VAS scores computing various anxiety aspects were comparable between the groups. However, subsequent VAS scores (measured at second time-point) declined to a greater extent in flupirtine treated patients, though significant in both the groups for most of the variables. Subsequent VAS scores also achieved statistical significance in intergroup comparison, especially for variables with higher baseline values [Tables 2 and 3]. Concern regarding waiting period was minimal on the evening before surgery. No untoward side effects were observed in any of the patients, but a sound night sleep in flupirtine group.

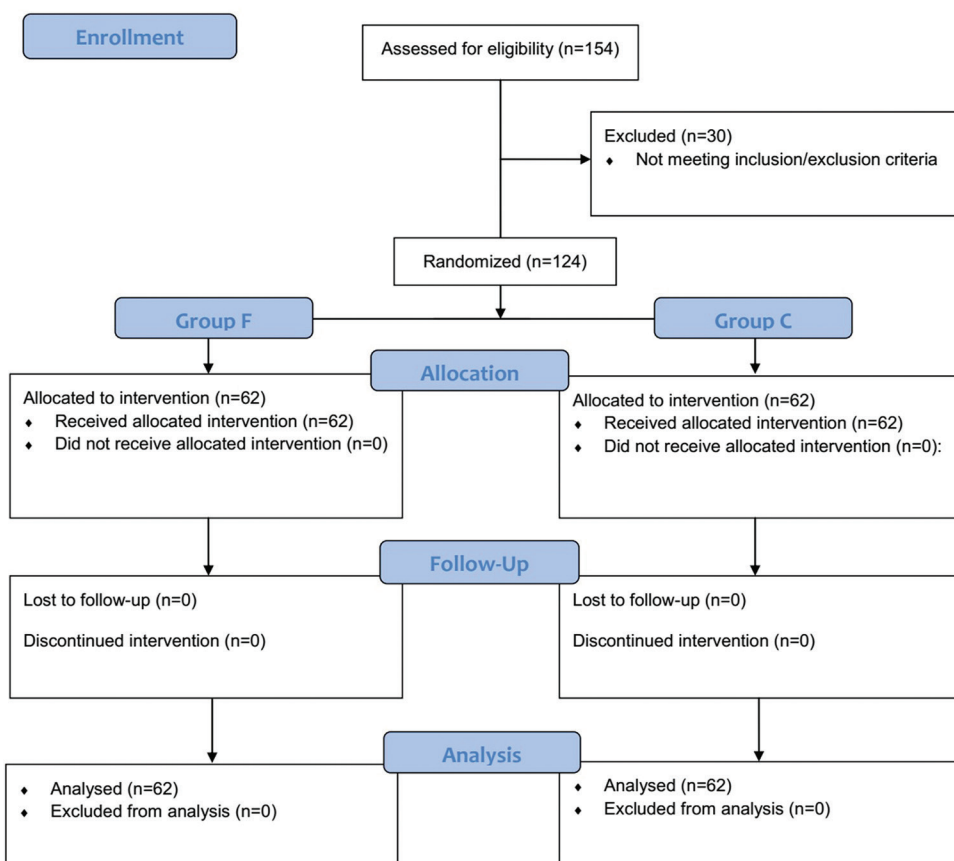


Figure 2: Flow chart of patients studied

Table 1: Demographic characteristics, and baseline anxieties with respective visual analog scale score (n=62)

Parameters	Group F	Group C	P
Age	40.72±10.11	37.94±12.05	0.14
Sex (male)	36	43	0.19
ASA physical status (I/II)	35/27	40/22	0.35
Preoperatively on anticonvulsants	42	45	0.55
Education (matriculation)	28	35	0.18
Previous anesthesia	12	8	0.20
Bad anesthesia experience	2	1	0.55
Information seeking behavior	30	36	0.28
Fear of anesthesia	44.38±15.03	41.20±14.91	0.25
Fear of surgery	75.74±8.11	73.15±14.73	0.23
Waiting for operation	32.71±10.30	35.92±15.09	0.15
At mercy of medical staff	61.44±18.95	57.84±18.86	0.32
What occur during anesthesia	38.31±16.13	35.12±12.36	0.22
Awareness during anesthesia	42.98±14.35	39.20±19.18	0.21
Result of operation	70.38±20.50	74.79±24.97	0.31
Not awakening after surgery	78.21±14.07	75.82±16.49	0.47
Time after awakening after surgery	48.16±17.33	50.14±22.90	0.74
Harm from surgery/anesthesia	75.40±22.38	72.81±16.02	0.57
Postoperative pain	25.09±13.27	28.89±14.71	0.10
Postoperative nausea/vomiting	34.83±18.43	31.64±17.50	0.37

Data expressed as numbers or mean±SDs of VAS. P<0.05 was considered significant. ASA: American society of Anesthesiologists; VAS: Visual analog scale; SDs: Standard deviations

Table 2: Comparison of specific anxieties among the groups after drug administration (n=62)

Parameters	Group F	Group C	P
Fear of anesthesia	23.74±8.15	30.28±7.27	<0.001
Fear of surgery	30.90±7.46	42.20±12.01	<0.001
Waiting for operation	14.71±10.21	12.92±9.14	0.35
At mercy of medical staff	24.62±8.19	31.14±15.21	<0.001
What occur during anesthesia	20.09±6.02	30.85±14.37	<0.001
Awareness during anesthesia	25.45±6.78	31.64±12.72	<0.001
Result of operation	32.30±12.88	44.73±26.32	<0.001
Not awakening after surgery	30.95±15.36	43.14±20.51	<0.001
Time after awakening after surgery	25.86±12.43	35.54±16.34	<0.001
Harm from surgery/anesthesia	30.40±22.38	42.18±17.62	<0.001
Postoperative pain	21.53±7.04	26.52±9.58	<0.001
Postoperative nausea/vomiting	23.07±6.93	28.32±8.06	<0.001

Data expressed as mean±SDs of VAS. P<0.05 was considered statistically significant. VAS: Visual analog scale; SDs: Standard deviations

### Discussion

Our investigation indicates a significant anxiolytic activity of flupirtine in reducing preoperative anxiety of patients enrolled for elective craniotomy as per study protocols. Flupirtine, a centrally-acting nonopioid analgesic, has selective neuronal potassium channel (Kv7) opening

**Table 3: Change in specific anxieties within groups after drug administration (n=62)**

Parameters	Group	Baseline	Second time-point	P
Fear of anesthesia	F	44.38±15.03	23.74±8.15	<0.001
	C	41.20±14.91	30.28±7.27	<0.001
Fear of surgery	F	75.74±8.11	30.90±7.46	<0.001
	C	73.15±14.73	42.20±12.01	<0.001
Waiting for operation	F	32.71±10.30	14.71±10.21	<0.001
	C	35.92±15.09	12.92±9.14	<0.001
At mercy of medical staff	F	61.44±18.95	24.62±8.19	<0.001
	C	57.84±18.86	31.14±15.21	<0.001
What occur during anesthesia	F	38.31±16.13	20.09±6.02	<0.001
	C	35.12±12.36	30.85±14.37	0.04
Awareness during anesthesia	F	42.98±14.35	25.45±6.78	<0.001
	C	39.20±19.18	31.64±12.72	0.001
Result of operation	F	70.38±20.50	32.30±12.88	<0.001
	C	74.79±24.97	44.73±26.32	<0.001
Not awakening after surgery	F	78.21±14.07	30.95±15.36	<0.001
	C	75.82±16.49	43.14±20.51	<0.001
Time after awakening after surgery	F	48.16±17.33	25.86±12.43	<0.001
	C	50.14±22.90	35.54±16.34	<0.001
Harm from surgery/ anesthesia	F	75.40±22.38	30.40±22.38	<0.001
	C	72.81±16.02	42.18±17.62	<0.001
Postoperative pain	F	25.09±13.27	21.53±7.04	0.03
	C	28.89±14.71	26.52±9.58	0.32
Postoperative nausea/vomiting	F	34.83±18.43	23.07±6.93	<0.001
	C	31.64±17.50	28.32±8.06	0.16

Data expressed as mean±SDs of VAS.  $P < 0.05$  was considered statistically significant. VAS: Visual analog scale; SDs: Standard deviations

properties.<sup>[5]</sup> Neuronal Kv7 channels are known to be potential drug targets in the treatment of various neuronal hyper-excitability conditions such as epilepsy, manic disorder, and neonatal seizures.<sup>[8,9]</sup> Various experimental models have observed similar hyperactivity in amygdala under the state of anxiety.<sup>[6,10]</sup> Hence, flupirtine as a neuronal Kv7 channel opener probably inhibited this hyperactivity by hyperpolarization of neuronal membrane and thus, reduced the severity of preoperative anxiety.<sup>[4]</sup> These findings are further supported by a previous trail demonstrating anxiolytic effects of flupirtine in albino rats without untoward side effects.<sup>[6]</sup>

Preoperative anxiety may be evaluated by both objective and subjective methods. Subjective assessments are though erroneous as clinicians often miscalculate the severity of patient anxiety. Among the various objective methods, we utilized “visual analog score” on account of its simplicity and reliability equivalent to standard “Spielberger State-Trait Anxiety Inventory” as shown by literature.<sup>[7]</sup> Among the various contributing factors, patients were more fearful of surgical aspects in comparison to anesthetics considerations. Other concerns included issues related to mercy of medical

staff during the period of surgery, harmful effects from anesthesia or surgery, fear about surgical outcome, and not awakening after surgery. Similar observations are reported in literature with few additions, including the waiting period for operation, awareness during anesthesia and postoperative complications.<sup>[7,11]</sup>

Anxiety variables were significantly lowered by both flupirtine and placebos, but this decline was much higher for flupirtine-treated patients. The decrease of anxiety scores in placebo group could be attributed to preoperative counseling, as every effort was undertaken to clear patient doubts and fear about the related issues; it was performed as a part of the standard institutional protocol in all recruited patients. The importance and efficacy of preoperative counseling has been similarly signified by previous trials on various ethnic groups.<sup>[12,13]</sup> This study highlights the augmented anxiolytic effect with flupirtine reflected as lower VAS scores of various anxiety variables, measured on the evening before surgery.

Flupirtine being freely soluble in water undergoes rapid gastric absorption and appears within 15–30 min in plasma after oral administration. Plasma flupirtine concentrations exhibit linear kinetics over the entire clinical dose range, but steady plasma levels are only achieved after 2 days of drug administration (75 or 150 mg twice daily) in healthy human volunteers.<sup>[5]</sup> As its anxiolytic doses are not yet defined, we initiated flupirtine at minimum effective analgesic dose (100 mg) and administered five such doses at 12 h intervals. We desired to achieve a steady plasma concentration of flupirtine before assessing its preoperative anxiolytic effects.

Flupirtine is well tolerated if administered on a short-term basis. Commonly reported side effects with continued administration include sedation, gastrointestinal upset, headache, disorientation, and hallucinations.<sup>[5,14]</sup> We observed no significant side effects but a sound night sleep in the flupirtine-treated patients. Similar observations were noted in a previous trial showing no other side effects except for sedation, with a bolus dose of 200 mg.<sup>[15]</sup>

A few limitations of this study included the lower intellectual level and illiteracy in many patients, failing which their rating, interpretation, and description of VAS anxiety score were assumptive at times even after appropriate preoperative counseling. We preferred to quantify the anxiolytic effects of flupirtine under the standard analgesic doses to develop better understanding about its efficacy as a premedication serving multiple purposes. Performing a dose-response study could, however, better delineate its optimal anxiolytic

effects. Future studies can investigate these aspects or utilize multimodal drug approach to reduce preoperative anxiety.

## Conclusion

This study provides an insight into the anxiolytic effects of flupirtine in the management of preoperative anxiety. It could be a vital addition to the counseling procedure directed to minimize the preoperative patient anxiety, subjected to further trials concentrating on its dose-response effects.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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