Original Research Article

Role of flupirtine in reducing preoperative anxiety of patients undergoing brain tumor surgery- A prospective double blind study

Shaileshkumar Modi1, Sunita Sharma1,*, Durga Jethava1

1 Dept. of Anaesthesiology and Critical Care Management, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India

1. Introduction

Perioperative anxiety is defined as a vague, unpleasant sensation that, as a result of sympathetic, parasympathetic, and endocrine stimuli, is often unspecific and unknown to the person and known to cause abnormal hemodynamics,1 difficult to manage pain after surgery.2

Furthermore, it may lead to increased doses of anesthetic induction agents, poor and delayed recovery.3 As per recent studies, Preoperative anxiety is an autonomous predictor of postoperative morbidity and mortality with survival analysis, including late mortality.4

As per some studies, the total incidence of preoperative anxiety in the western world is between 60% to 80%, but some researches have shown a wider variation of 11%-80%.5 Thus it must be considered as an important factor to treat it.

Various studies have been conducted to test the effect of specific interventions on preoperative anxiety such as preoperative information,6 continuous information,7 nursing interventions, music,8 or anxiolytic premedication.9

As per various clinical and preclinical researches on anxiety, increased activity of amygdala has been mentioned thus neuronal kv7 channels can be a potential target for anxiolytic medications. Flupirtine acts as N- methyl-d-aspartate antagonism and stimulates neuronal kv7 channels causing analgesic action which has better tolerability, preservation of respiratory functions, analgesic actions and antiepileptic properties.10

Previous clinical trials have reported flupirtine’s anxiolytic activity in animal models.11 Flupirtine has

---

*Corresponding author.
E-mail address: drsunitasharma43@gmail.com (S. Sharma).
neuroprotective and anticonvulsant properties. Limited studies have been done to evaluate the anxiolytic properties of flupirtine. Thus we conducted a study to evaluate the role of flupirtine on preoperative anxiety in patients undergoing brain tumour surgery.

2. Materials and Methods

This prospective, randomized, double-blinded, placebo-controlled study was done after ethical committee permission in patients undergoing intracranial space-occupying lesions after obtaining informed consent. Patients whose ages between 18-65-year-old with either sex, ASA class I/II, and conscious and oriented were included in our study. Patient with a history of drug allergy, history of psychiatric illness, pregnancy, end-organ failure was excluded from our study. All patients (100 patients) were randomly divided into two groups, group X (flupirtine Group) and group Y (placebo control), by using the chit-box method. Each patient has been thorough pre-anaesthetic examination and counselling. Flupirtine group and control group received capsule flupirtine (Lupirtine) 100mg and capsule starch orally as per drug regimen described below. All routine laboratory test including hemogram, coagulogram, biochemical indices, X-Ray chest, ECG and other necessary investigation was done.

After pre-operative counselling and obtaining informed consent, study drug was given 38 hours pre-operatively followed by three subsequent doses thereafter 12 hours apart. The last dose was given two hours before surgery.

On 12 point questionnaire, all enrolled patients were instructed to state their anxiety level in form of visual analogue scale (VAS), which was noted twice: just before pre-operative counselling which was considered as a baseline value, and 2 hours after the last dose of the studied drug which was considered as a second-time point.

A questionnaire was given to all patients which included twelve objectives. Out of twelve objectives, two objectives were to assess overall fear of anaesthesia and ten objectives were to assess various other factors which contribute to pre-operative anxiety. These questionnaires are described as per below.

A visual analogue scale was used to evaluate anxiety. It contained twelve objectives as per described below.

1. Fear of anaesthesia
2. Fear of surgery
3. Waiting for operation
4. At mercy of medical staff
5. What occur during anaesthesia
6. Awareness during Anaesthesia
7. Result of an operation
8. Not awakening after surgery
9. Time after awakening after surgery
10. Harm from surgery/Anaesthesia
11. Postoperative Pain
12. Postoperative Nausea/Vomiting

2.1. Visual analogue scale

A visual analogue scale is a measuring instrument designed to measure a feature or position which is thought to extend across a continuum of values and is not readily measured.

In operational terms, VAS generally is a 100 mm horizontal line, in which left end denotes "no anxiety", whereas the right denotes "maximum anxiety". A comparison between organizations will also be noticed of different patient characteristics influencing the preoperative anxiety.

2.2. Statistical analysis

Collected data were Microsoft Excel and analysed using Epi Info 7.1 and analysed in term of Mean and Standard Deviation. Unpaired T-test was used for comparison of various aspects of two groups. Paired T-test was used for within-group comparison. Chi-square and Fisher exact tests were performed to test for differences in proportions of categorical variables between two groups. The level P < 0.05 was considered as the cut-off value or significance.

3. Results

Demographic Data were recorded in terms of Age, Sex and ASA grades were comparable (Table 1).

Visual analog scale values at baseline in both groups for different parameters were comparable. VAS for Fear for surgery, Result of operation, Not awakening after surgery and Harm from surgery/Anaesthesia were higher than for other parameters at baseline (Table 2).

Significant reduction of VAS was observed at second point time for fear of anaesthesia, Fear of surgery, at mercy of medical staff, what occur during anaesthesia, awareness during anaesthesia, result of an operation, Not awakening after surgery, time after awakening after surgery. Harm from surgery/anaesthesia, postoperative nausea/vomiting in flupirtine group compare to placebo group (Table 3).

Significant reduction in VAS for specific anxiety for within-group comparison in both flupirtine group and placebo group. but the reduction was not significant for what occur during anaesthesia and postoperative nausea/vomiting in the placebo group (Table 4).

4. Discussion

The prevalence of preoperative anxiety as per studies ranges from 60% to 80% in western countries. But as per some researches, it has a wider range from 11% to 80%. As per the study of Perks Anna et al., Incidence of preoperative anxiety in patients undergoing neurosurgery was 89%. In our study level of preoperative anxiety in patients undergoing brain
Table 1: Demographic variables in both groups

| Variable               | Group X          | Group Y          | P value |
|------------------------|------------------|------------------|---------|
| AGE (years) Mean±SD    | 39.38±13.86      | 40.90±11.88      | 0.2788  |
| Gender (male/female) (n=50) | 20/30           | 21/29            |         |
| ASA grade (I/II) (n=50) | 24/26            | 27/23            | 0.6893  |

SD- Standard Deviation

Table 2: Baseline V AS in both groups for various parameters

| Baseline VAS Parameters | Group X          | Group Y          | P value |
|-------------------------|------------------|------------------|---------|
| Fear of Anaesthesia     | 50.09±13.69      | 45.8±13.75       | 0.066   |
| Fear of Surgery         | 75.2±11.95       | 75.10±15.4       | 0.971   |
| Waiting for operation   | 39.30±10.74      | 40.98±13.4       | 0.491   |
| At mercy of medical staff| 43.20±12.69     | 38.90±13.18      | 0.100   |
| What occur during Anaesthesia | 36.90±15.48   | 40.80±14.33      | 0.194   |
| Awareness during Anaesthesia | 44.10±12.96  | 40.70±12.50      | 0.185   |
| Result of operation     | 76.70±21.84      | 76.97±19.23      | 0.970   |
| Not awakening after surgery | 84.00±12.62   | 78.20±15.64      | 0.044   |
| Time after awakening after surgery | 38.50±14.47 | 36.10±14.72      | 0.413   |
| Harm from Surgery/ Anaesthesia | 78.15±17.09 | 82.39±17.55      | 0.183   |
| Postoperative pain      | 30.34±13.96      | 27.30±11.53      | 0.238   |
| Postoperative Nausea/ V omitting | 31.10±14.65 | 28.03±13.21      | 0.353   |

Table 3: Second point time V AS for various parameters in both groups

| Second point time VAS Parameters | Group X          | Group Y          | P value |
|----------------------------------|------------------|------------------|---------|
| Fear of Anaesthesia              | 25.90±8.06       | 33.20±9.24       | 0.00    |
| Fear of Surgery                  | 31.39±9.60       | 47.10±13.14      | 0.00000 |
| Waiting for operation            | 15.50±7.37       | 14.60±9.29       | 0.59175 |
| At mercy of medical staff        | 19.60±10.19      | 30.70±9.31       | 0.00000 |
| What occur during Anaesthesia    | 18.50±10.98      | 37.60±10.16      | 0.00000 |
| Awareness during Anaesthesia     | 19.00±7.95       | 33.70±11.01      | 0.00000 |
| Result of operation              | 37.2±9.32        | 53.60±16.20      | 0.00000 |
| Not awakening after surgery      | 36.10±11.03      | 47.10±14.22      | 0.00004 |
| Time after awakening after surgery | 22.20±10.84    | 28.20±9.99       | 0.00491 |
| Harm from Surgery/ Anaesthesia   | 35.20±16.07      | 45.80±11.62      | 0.00027 |
| Postoperative pain               | 20.10±7.39       | 22.80±9.70       | 0.12056 |
| Postoperative Nausea/ V omitting | 20.10±8.42       | 25.80±10.37      | 0.00301 |

tumour surgery by using V AS was 52, which was similar to the study of Perks Anna et al.\textsuperscript{14} and Perks Anna et al. considered it a higher level of anxiety compared with previous studies.

In the study of Williams JB et al.,\textsuperscript{15} they found that a high level of anxiety is a strong predictor of increased risk of major morbidity and mortality. Shailendra Sigdel et al.\textsuperscript{16} conducted a short review of Perioperative anxiety. They have mentioned psychological response to anxiety which includes major cardiac events (acute myocardial infarction, heart failure, pulmonary oedema), high readmission rate (1st 6 month, 1 years), poor quality of life, high rate of cardiac mortality, high postoperative pain, increased analgesic and anaesthetic consumption, prolonged hospital stay, adverse influence during anaesthetic induction and patient recovery and decrease patient satisfaction with perioperative experience. Because of the detrimental effects of preoperative anxiety as mentioned by the above studies, it should be treated for better outcomes of procedure or surgery, especially in Neurosurgery.

As per mentioned in the study of Kim Lawson,\textsuperscript{17} Flupirtine has anticonvulsant and neuroprotective properties, which are suggestive of its use in various neurological diseases such as Parkinson’s disease, Alzheimer’s disease, creutzfeldt-jackob disease, age-related macular degeneration, batten disease, and prion disease. With its neuroprotective action flupirtine also shows anticonvulsant activities. This effect of flupirtine may be due to suppression of the neuronal hyperexcitability by the stimulation of Kv channels which was demonstrated by the antiepileptic drug development program. As per some study, flupirtine is as effective as phenobarbital and diazepam.
Table 4: Change in specific anxiety within groups before and after drug administration

| Parameters                           | Group | Baseline          | 2nd point time     | P value  |
|--------------------------------------|-------|-------------------|--------------------|----------|
| Fear of Anaesthesia                  | X     | 50.09±13.69       | 25.90±8.06         | 0.00000  |
|                                      | Y     | 45.8±13.75        | 33.20±9.24         | 0.00000  |
| Fear of Surgery                      | X     | 75.2±11.95        | 31.39±9.60         | 0.00000  |
|                                      | Y     | 75.10±15.44       | 47.10±13.14        | 0.00000  |
| Waiting for operation                | X     | 39.30±10.74       | 15.50±7.37         | 0.00000  |
|                                      | Y     | 40.98±13.44       | 14.60±9.29         | 0.00000  |
| At mercy of medical staff            | X     | 43.20±12.69       | 19.60±10.19        | 0.00000  |
|                                      | Y     | 38.90±13.18       | 30.70±9.31         | 0.00085  |
| What occur during Anaesthesia        | X     | 36.90±15.48       | 18.50±10.98        | 0.00000  |
|                                      | Y     | 40.80±14.33       | 37.6±10.16         | 0.16762  |
| Awareness during Anaesthesia         | X     | 44.10±12.96       | 19.00±7.95         | 0.00000  |
|                                      | Y     | 40.70±12.50       | 33.70±11.01        | 0.00164  |
| Result of operation                  | X     | 76.70±21.84       | 37.2±9.32          | 0.00000  |
|                                      | Y     | 76.97±19.23       | 53.60±16.20        | 0.00000  |
| Not awakening after surgery          | X     | 84.00±12.62       | 36.10±11.03        | 0.00000  |
|                                      | Y     | 78.20±15.64       | 47.10±14.22        | 0.00000  |
| Time after awakening after surgery   | X     | 38.50±14.47       | 22.20±10.84        | 0.00000  |
|                                      | Y     | 36.10±14.72       | 28.20±9.99         | 0.00347  |
| Harm from Surgery/ Anaesthesia       | X     | 78.15±17.09       | 35.20±16.07        | 0.00000  |
|                                      | Y     | 82.39±17.55       | 45.80±16.62        | 0.00000  |
| Postoperative pain                   | X     | 30.34±13.96       | 20.10±7.39         | 0.00001  |
|                                      | Y     | 27.30±11.53       | 22.80±9.70         | 0.04846  |
| Postoperative Nausea/ Vomiting       | X     | 31.10±14.65       | 20.10±8.42         | 0.00003  |
|                                      | Y     | 28.03±13.21       | 25.80±10.37        | 0.32378  |

in seizures in neonates produced by chemoconvulsant, ischemic injury or hypoxic injury.

There are various methods to treat preoperative anxiety which also includes drugs. These include benzodiazepines that modulate γ2-subunit of GABA receptors, while flupirtine acts on δ-subunit of GABA receptors which are extremely sensitive towards neurosteroid and stimulation of kv channels.

Korsgaard MP et al.10 (2005) mentioned that neuronal Kv7 channels are a target for developing novel anxiolytics after in vitro and in vivo studies provide compelling evidence. Jyothi et al. also mentioned the anxiolytic properties of flupirtine in albino rats. Thus we have considered flupirtine as an anxiolytic in our study.

There are various methods to measure the anxiety level in patients undergoing procedure or surgery. The visual analogue scale is a simple, reliable, and as effective as state anxiety score of STAI to evaluate anxiety level inpatient undergoing surgery which has been mentioned by kindler et al... Davey et al.18 (2007) also found that both visual analogue scale and Likert scale are as effective as STAI. They further concluded that both measurements provides a quick and straightforward assessment of anxiety with limited time and decreases the burden to answer many questions on patients.

In our study patients were more feared for surgery-related factors than anaesthesia related factors similar results were observed in the study of Ghanshyam et al. and Perk Anna et al... Compared to baseline significantly reduction of VAS was observed in both group but the reduction of VAS was more significant in the flupirtine group compared to the placebo group. Reduction of VAS in the placebo group might be due to preoperative counselling. Overall reduction of VAS in flupirtine group was 27%. Compared to our study in the study of D Ionescu et al.19 overall reduction of VAS by oral melatonin (3mg) and oral midazolam (3.75mg) were 17% and 22% respectively. There were no side effects observed during the study.

5. Conclusion
Flupirtine and the preoperative counselling can be a novel approach to reduce preoperative anxiety and its outcome in neurosurgical patients without any major side effects.

6. Source of Funding
None.

7. Conflict of Interest
None.

References
1. Inna M, Zeen NK. Preoperative Anxiety and Intraoperative Anesthetic Requirements. Surv Anesthesiol. 2000;44:272–3.
2. Anderson KO, 3rd FTM. Psychological preparation for invasive medical and dental procedures. J Behav Med. 1983;6:1–40.
3. Akinsulure A, Owojuyigbeam, Faponle AF, Fatoye FO. Assessment of preoperative and postoperative anxiety among elective major surgery patients in a tertiary hospital in Nigeria. *Middle East J Anesthesiol*. 2015;23(2):235–40.

4. Woldegerima YB, Fitwi GL, Yimer HT, Hailekiros AG. Prevalence and factors associated with preoperative anxiety among elective surgical patients at University of Gondar Hospital. Gondar, Northwest Ethiopia, 2017. A cross-sectional study. *Int J Surg Open*. 2018;10:21–9.

5. Nigussie S, Belachew T, Wolancho W. Predictors of preoperative anxiety among surgical patients in Jimma University Specialized Teaching Hospital, South Western Ethiopia. *BMC Surg*. 2014;14(1):1–10.

6. Szöllősi M, Nordahl G, Olofsson N, Asplund K. The impact of preoperative information on state anxiety, postoperative pain and satisfaction with pain management. *Patient Educ Couns*. 2003;51(2):169–76.

7. Haugen AS, Eide GE, Olsen MV, Haukeland B, Remme ÅR, Wahl AK. Anxiety in the operating theatre: a study of frequency and environmental impact in patients having local, plexus or regional anaesthesia. *J Clin Nurs*. 2009;18(16):2301–10.

8. White JM. Effects of relaxing music on cardiac autonomic balance and anxiety after acute myocardial infarction. *Am J Crit Care*. 1999;8(4):220–30.

9. Carroll JK, Cullinan E, Clarke L, Davis NF. The role of anxiolytic premedication in reducing preoperative anxiety. *Br J Nurs*. 2012;21(8):479–83.

10. Korsgaard MPG, Hartz BP, Brown WD, Ahring PK, Strøbek D, Mirza NR. Anxiolytic Effects of Maxipost (BMS-204352) and Retigabine via Activation of Neuronal Kv7 Channels. *J Pharmacol Exp Ther*. 2005;314(1):282–92.

11. Jyothi CH, Santhosh R, Gokul CG, Kiran LJ, Narendranath S, Acharya A. A study on anxiolytic effect of flupirtine in albino rats. *J Pharm Res*. 2012;5:1624.

12. Friedel HA, Fitton A. Flupirtine. *Drugs*. 1993;45(4):548–69.

13. Kindler CH, Harms C, Amsler F, Ihde-Scholl T, Scheidegger D. The Visual Analog Scale Allows Effective Measurement of Preoperative Anxiety and Detection of Patients’ Anesthetic Concerns. *Anesth Analg*. 2000;90(3):706–12.

14. Perks A, Chakravarti S, Manninen P. Preoperative Anxiety in Neurosurgical Patients. *J Neurosurg Anesthesiol*. 2009;21(2):127–30.

15. Williams JB, Alexander KP, Morin JF. Preoperative anxiety as a predictor of mortality and major morbidity in patients aged >70 years undergoing cardiac surgery. *Am J Cardiol*. 2013;111(1):137–42.

16. Sigdel S. Perioperative anxiety: A short review. *Glob Anesth Perioper Med*. 2015;1(4):107–8.

17. Lawson K. Pharmacology and clinical applications of flupirtine: Current and future options. *World J Pharmacoal*. 2019;8(1):1–13.

18. Davey HM, Barratt AL, Butow PN, Deeks JJ. A one-item question with a Likert or Visual Analog Scale adequately measured current anxiety. *J Clin Epidemiol*. 2007;60(4):356–60.

19. Ionescu D, Bădescu C, Ilie A, Michutia I, Ianuc C, Ion D, et al. Melatonin as premedication for laparoscopic cholecystectomy: a double-blind, placebo-controlled study. *South Afr J Anaesth Analg*. 2008;14(4):8–11.

Author biography

Shaileshkumar Modi PG Resident

Sunita Sharma Assistant Professor

Durga Jethava Professor and HOD

Cite this article: Modi S, Sharma S, Jethava D. Role of flupirtine in reducing preoperative anxiety of patients undergoing brain tumor surgery- A prospective double blind study. *Indian J Clin Anaesth*. 2020;7(3):416–420.