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EFFECTS OF ORAL LORAZEPAM VERSUS ORAL ALPRAZOLAM ON THE POSTOPERATIVE COGNITIVE FUNCTION

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ABSTRACT

Objectives: To compare the effect of oral Lorazepam 1 mg or oral alprazolam 0.5 mg given at night before surgery on cognitive function in patients undergoing elective general surgery receiving general anaesthesia.

Methodology: In a prospective double-blind manner 128 patients aged 30 to 50 years belonging to ASA I and II scheduled for elective surgery under general anaesthesia were randomly divided into two equal groups. Group A (n=64) received oral lorazepam 1 mg and Group B (n=64) received oral alprazolam 0.5 mg). Cognitive function were assessed by 1. Rey's Auditory Verbal Learning test, (RAVLT) test to assess the ability to form new verbal memory, 2. Trail Making Test (TMT) part A to assess psychomotor ability and 3. Digit Span Test to assess short term verbal memory. These were assessed thrice: 1) during preoperative assessment, 2) 30 minutes before induction and 3) 30 minutes after reversal of general anaesthesia,

Results: Oral alprazolam affected cognitive processing speed more than oral lorazepam and the association was statistically significant (P-value <0.05) in one of the three tests performed. Other two tests showed statistically insignificant results.

Conclusion: Lorazepam might be a better anxiolytic premedicant than alprazolam.

KEYWORDS : anxiolytic, alprazolam, lorazepam, cognitive function

INTRODUCTION:

Oral anxiolytic medications are routinely used in patients planned for any elective surgery. Oral benzodiazepines like Diazepam, Alprazolam, Lorazepam etc. are the most common drugs used for this purpose. However, these drugs are known to impair cognitive function temporarily particularly those involving psychomotor domain function. They are known to interfere with short term memory and may cause temporary anterograde amnesia.[1,2]

Postoperative cognitive dysfunction (POCD) is a short term decline in cognitive function (especially in memory and executive function) that may last for a few days to few weeks after surgery. In rare cases, this disorder may persist for several months after major surgery. [3] The cause may be a number of factors. One of its causes include the use of anxiolytics before surgery.

The incidence of POCD varies widely across studies even though the conduct of study and anesthesia may be similar. Besides individual patient differences methodology issues such as choice of test battery, time of postoperative assessment and method of analysis to determine post-operative cognitive dysfunction may be sources of difference.[4]

Neuropsychological testing are commonly used to measure cognitive function. [4] These cover a range of cognitive domain such as memory, attention span, concentration and perceptual abilities.

The causes of POCD are not adequately understood. It does not appear to be caused by lack of oxygen or impaired blood flow to the brain and is equally likely under regional and general anesthesia. It may be mediated by the body's inflammatory response to surgery. POCD is associated with poorer recovery and increased utilization of social and financial assistance.[5,6,7]

Although the anxiolytic efficacy of oral benzodiazepines have been well studied by numerous authors, robust evidence is still lacking regarding the effects of oral benzodiazepines as anxiolytic premedication on the preoperative and postoperative cognitive function in patients undergoing elective major surgery under general anesthesia.

This study was aimed at comparing the cognitive function before and after elective major non cardiac surgery under general anesthesia in patients receiving preoperative lorazepam 1 mg or alprazolam 0.5 mg on the night before surgery.

AIMS AND OBJECTIVES:

The aim of this study is to compare the effects of anxiolytic premedication taken night before surgery with oral Lorazepam 1 mg or oral Alprazolam 0.5 mg on the cognitive function of patients undergoing elective surgical procedures.

SPECIFIC OBJECTIVES:

To compare 1) the preoperative (30 minutes before induction of anesthesia) cognitive function and 2) the postoperative (30 minutes after recovery from anesthesia) cognitive function, as measured by a set of psychometric tests, in groups of patients treated with oral Lorazepam 1 mg or oral alprazolam 0.5 mg given at 9 P.M. on the night before surgery.

Study period:

One year (January - December 2017)

Study sample:

We planned a study of a continuous response variable from independent control and experimental subjects with one control(s) for experimental subject. We selected a standard deviation of 1.0 as per literature review from previously done similar studies.[7,8] Literature review also revealed the difference of approximately 0.5(approx.) when equipotent dose of these drugs were administered and compared. [9, 10] So, as per software-based calculation, we needed to study 128 patients with either of tab. alprazolam (0.5 mg) or tab. lorazepam (1mg) [allocation ratio of 1:1] to be able to reject the null hypothesis so that the population means of both groups were equal with probability (power) 0.8.[11] The Type 1 error probability associated with this test of the null hypothesis is 0.05.

Sample Design:

Prospective, randomized, double-blind study.

Parameters to be studied:

The cognitive function of study participants was measured preoperatively and postoperatively to assess the effects of lorazepam (1 mg) and alprazolam (0.5 mg) as anxiolytic premedication. The following were named as core test in a consensus recommendation on POCD issued in 1995:

A. Rey's Auditory Verbal Learning test, (RAVLT) test to assess the ability to form new verbal memory.[12]
B. The Trail Making Test, TMT, part A, psychomotor ability test.[12]
C. The Digit Span Test, DST, short term verbal memory test.[12]

Procedure of each neuropsychometric test:

A. Rey Auditory Verbal Learning Test (RAVLT), NIH Toolbox version:

Figure 1: Table for data collection by Rey's Auditory Visual Learning test

REY AUDITORY VERBAL LEARNING TEST (RAVLT)

Patient:

Age:

LIST A	1	2	3		
DRUM					
CURTAIN					
BELL					
COFFEE					
SCHOOL					
PARENT					
MOON					
GARDEN					
HAT					
FARMER					
NOSE					
TURKEY					
COLOR					
HOUSE					
RIVER					
SCORE					

The Rey's Auditory Visual Learning Test is a word-list learning task in which 15 unrelated words are presented orally (via audio recording) over three consecutive learning trials to the patient. After each presentation, the participant is asked to recall as many of the words as he/she can. The RAVLT is scored by taking the sum of the number of words recalled across the three learning trials (possible range is 0-45 words). The raw score is used for interpretation of the Rey's test, with higher scores representing better episodic memory.[13]

B. Trail Making Test (TMT), Parts A & B:

Figure 2: Table for data collection by Trail Making Test Part A

The Trail Making Test is a neuropsychological test of visual attention and task switching. It consists of two parts in which the subject is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy.[1] The test can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning.

Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25 and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient drew lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). Each patient was instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient made an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors was included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.[14] In view of the expected lower levels of education in our institution, only part A of the test was done for the patients for this study because of its simplicity and ease of application. The first part was used primarily to examine cognitive processing speed.

C. Digit Span Test:

Figure 3: Sequence of numbers for data collection by Digit Span Test

Digit-Span Test

1. 590
2. 4861
3. 73094
4. 249658
5. 1468245
6. 39215760
7. 625739184
8. 0638941725

This test measures verbal working memory ability (short-term verbal memory). Working memory is the ability of the brain to "hold on" to information that is needed to complete complex tasks.

The study participant was instructed to listen carefully to audio record of a series of numbers and asked to repeat them immediately in the same order as in the audio record. Each number was said in a monotone voice, one second apart in the audio record. The first series was three numbers, e.g. "3, 9, 2." The person repeats those numbers back to the observer. The next record is a series of four numbers, e.g. "4, 7, 3, 1." Again, the participant repeated those immediately after listening. The test was continued in the same manner by increasing the series of numbers to five digits, six digits and so forth until the participant made a mistake.[15]

STUDY TECHNIQUE:

After obtaining permission from the institutional ethical committee total of 128 consented participants aged 30 to 50 years of ASA I and II undergoing elective noncardiac surgical procedure at Medical College, Kolkata were randomly divided into two groups-Group-A-receiving lorazepam 1mg (n=64) and Group B receiving oral alprazolam 0.5 mg (n=64) at night before surgery.

The medications were administered in a double blinded manner by the ward nurse or anesthesia trainee, taking care to ensure that the patient, the preoperative and postoperative assessors were not aware of the exact identity of the drug administered.

For Rey Auditory Verbal Test, prerecorded audio of sequence of words in a standardized pitch, volume and speed of articulation were used. For Trail Making Test, pre-printed papers for trail making by the patient were used. For Digit Span Test, pre-recorded audio of sequence of numbers in a standardized pitch, volume and speed of articulation were used. The audio recording and playback system of a Smartphone were used for administering the auditory tests.

We compared oral lorazepam 1 mg and oral alprazolam 0.5mg, since it is known that oral lorazepam 1 mg is equivalent to oral alprazolam 0.5 mg.

On the day before surgery at the Pre anesthesia clinic, a short psychometric examination of the patient (comprising RAVLT, TMT and DST) were done and marks were given according to response.

On the day of surgery, 30 minutes before surgery a short psychometric examination of the patients (comprising RAVLT, TMT and DST) were done and marks were given according to response.

General anesthesia technique:

At the operating room, intravenous fluid was infused after intravenous cannulation. Standard monitors (ECG, pulse oximeter, NIBP cuffs) were attached to the patients. All patients were pre-medicated with antisialagogue glycopyrrolate 4 mcg/kg intravenously. After pre-oxygenation with 100% oxygen for 3 minutes, general anesthesia was induced with intravenous propofol 2 mg/kg administered over 20 seconds. Endotracheal intubation was facilitated with intravenous succinylcholine 1 mg/kg. Immediately after completion of tracheal intubation, intermittent positive pressure ventilation was started. General anesthesia was maintained with inhalational anesthetic sevoflurane and 40% oxygen in nitrous oxide. Surgical muscle relaxation was maintained with loading intravenous bolus of 0.5 mg/kg atracurium and 0.1 mg/kg at 30 minutes intervals. Intraoperative analgesia comprised intravenous tramadol 2 mg/kg and paracetamol 20 mg/kg infusion. Ringer lactate was infused to replace fasting fluid deficits and hourly maintenance fluid therapy. At the end of surgery, anesthetic agents were turned off and after spontaneous return of respiration reversal of neuromuscular paralysis was done with intravenous neostigmine (50 mcg/kg) and glycopyrrolate (10 mcg/kg).

At the 30 minute following reversal of patients from general anesthesia, each participant patient was reassessed by the same psychometric tests (comprising RAVLT, TMT and DST) and the marks calculated and noted in the case record form.

ANALYSIS OF DATA:

STATISTICAL ANALYSIS:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0 and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

Once a t value was determined, a p-value could be found using a table of values from Student's t-distribution. P-value $\leq$ 0.05 was considered for statistically significant.

RESULTS AND ANALYSIS:

Table 1: Demographic Parameters

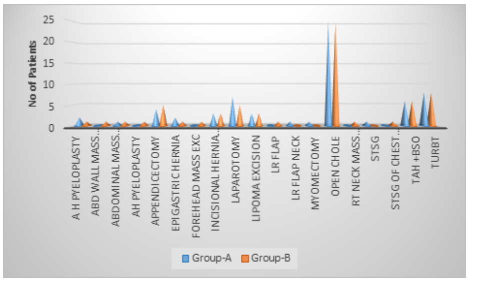
	Group A	Group B	P-value
Age(years)	42.11 ± 5.49	41.72 ± 6.00	0.70 (NS)
Sex (M: F)	25:39	11:21	0.58 (NS)
ASA I:II	53:11	27:5	0.81 (NS)

Group A= premedication with oral Lorazepam 1mg, Group B= premedication with oral Alprazolam 0.5mg

NS – Not statistically significant

The analysis showed two study groups were comparable for age, gender and physical status.

Figure 4: Distribution of patients according to surgery they underwent under general anesthesia in the two groups A&B.



Distribution of type of operation was not statistically significant in two groups. (p=0.9282).

Table 2: Stratified distribution of educational qualification in two study groups:

EDU.QUAL.	GROUP	NUMBER	%	P VALUE
CLASS V - IX	A	41	64.06	0.2492
	B	34	53.13	
CLASS X - XII	A	12	18.75	
	B	21	32.81	
BACHELOR	A	10	15.63	
	B	7	10.94	
MASTERS	A	1	1.56	
	B	2	3.12	

Distribution of educational status was not statistically significant in two groups. (p=0.2492)

Table 3: Distribution of mean RAVLT SCORE between group A and Group B:

RAVLT	Group A Score Mean ± SD	Group B Score Mean ± SD	P Value
PAC	20.8281 ± 3.5436	20.9844 ± 3.6406	0.8061
PRE OP	19.7188 ± 3.8851	19.0000 ± 3.9036	0.2985
POST OP	16.0000 ± 2.9277	16.2813 ± 3.1946	0.6045

Data was collected during three stages i.e. at pre anesthetic clinic (PAC), at 30 minutes before surgery (PREOP) and 30 minutes after reversal (POSTOP). Difference of mean RAVLT SCORE in two study groups during PAC at 30 minutes before (PRE OP) and 30 minutes after surgery (POST OP) was not statistically significant.

Table 4: Distribution of mean TMT A SCORE between the two groups - A & B

TMT A TEST	GROUP A SCORE MEAN ± SD	GROUP B SCORE MEAN ± SD	P VALUE
PAC	70.9531 ± 20.9197	70.4844 ± 19.5911	0.8961
PRE OP	77.7813 ± 26.9606	68.7656 ± 17.7315	0.0272
POST OP	126.8281 ± 30.1386	112.8281 ± 33.8833	0.0149

Distribution of TMT A score PAC was not significant (p=0.8961), but pre-operative and post-operative score in two groups was statistically significant (p=0.0272) and (p=0.0149).

Table 5: Distribution of DST SCORE PAC in two groups and result expressed as percentage

DST PAC	Score	Number	%	P Value
Group A	4	8	12.50	0.8478
	5	44	68.80	
	6	12	18.80	
Group B	4	6	9.40	
	5	46	71.90	
	6	12	18.80	

Chi-square value: 0.3302; p-value: 0.8478

Distribution of DST SCORE PAC was not statistically significant in two groups. (p=0.8478)

Table 6: Distribution of DST SCORE PRE in two groups and result expressed in percentage

DST PRE	Score	Number	%	P Value
Group A	4	10	15.60	0.0861
	5	35	54.70	
	6	19	29.70	
Group B	4	15	23.40	
	5	40	62.50	
	6	9	14.10	

Chi-square value: 4.9048; p-value: 0.0861
Distribution of DST SCORE PRE was not statistically significant in two groups. (p=0.0861)

Table 7: Distribution of DST SCORE Post in two groups and result expressed in percentage

DST POST	Score	Number	%	P Value
Group A	3	1	1.60	0.5717
	4	42	65.63	
	5	21	34.40	
	6	0	0.00	
Group B	3	1	1.60	
	4	41	64.10	
	5	20	31.30	
	6	2	3.10	

Chi-square value: 2.0035; p-value: 0.5717
Distribution of DST SCORE POST was not statistically significant in two groups. (p=0.5717)

DISCUSSION:

Postoperative cognitive dysfunction (POCD) is more common in elderly patients [16], patients undergoing cardiac surgery [17], patients undergoing prolonged surgery [16] and can also be seen following both general anesthesia and regional anesthesia[3].

There is a lack of clinical data regarding incidence of POCD in the age group of 18 to 60 years and those undergoing major surgery under general anesthesia of less than 3 hours duration. Thus this study would help us understand the phenomenon of POCD in this age group and the role of benzodiazepines in affecting memory and recall functions in these patient subgroups.

Difference of mean age, sex distribution and ASA physical status in two groups were not statistically significant. Educational qualification adversely affects cognitive function. [3, 18] Incidence of POCD was increased in patients with lesser level of education. When educational qualification was considered the two study groups were found to be matched.

Type of surgery affects cognitive function. Incidence of POCD is more common with cardiac surgery. [17] In non-cardiac surgery there is a definite incidence of cognitive dysfunction which increased with duration of surgery[16]. Also incidence of cognitive dysfunction is seen with both general anesthesia as well as regional anesthesia[3]. In the two groups studied here, the type of surgeries were well matched between the two groups (p-value=0.9282).

Neuropsychiatric tests were used to evaluate cognitive function in patients of the two groups [4]. A battery of 3 tests viz. Rey's Auditory Visual Learning test (RAVLT), Trail Making Test part A (TMT part A) and Digit Span Test (DST) were used to evaluate cognitive dysfunction in response to either alprazolam or lorazepam in the two groups.

Neuropsychiatric assessment was done 3 times in each patient. The results showed that there was no statistically significant difference between alprazolam and lorazepam group on testing of cognitive function by 2 of 3 of the above mentioned tests – viz. Rey's Auditory Visual Learning Test (RAVLT) and Digit Span Test (DST). The results are in keeping with the study done by Kumar R, Mac DS, Gabrielli WF, et al (1987).[9]

In case of the Trail Making Test part A, the results were statistically not significant (p-value>0.05) at the pre-anesthetic checkup (PAC). This meant that the two groups A & B were comparable to one another before the administration of any drug and that the patients had very little pre-existing cognitive impairment prior to appearance for the study. However, after the administration of the drugs neuropsychiatric testing with Trail Making Test Part A both preoperatively and postoperatively revealed that there was a statistically significant (i.e. p-value <0.05) impairment of cognitive function. Thus we can infer that tab. Alprazolam affected cognitive processing speed more than tab. Lorazepam and that the association is statistically significant (i.e. p-value<0.05).

LIMITATIONS OF THE STUDY

It includes age distribution of the patients studied (30 to 50 years – only middle-aged individuals were considered), shorter duration of surgery (less than 3 hours major non cardiac surgery under general anesthesia) and additive effect of other medications used during general anesthesia e.g. inhalational agents (Sevoflurane). Sevoflurane had been used during general anesthesia as inhalational agent for maintenance. As far as its effects are concerned, studies show that it is rapidly eliminated with minimal metabolic breakdown which may reduce cognitive dysfunction in surgical patients and facilitate a faster recovery after general anesthesia, provided the duration of surgery is not prolonged.[18]

Another limitation of this study is the fact that cognitive function recording was only taken 30 minutes after reversal from general anesthesia and no further recordings were taken after that. Cognitive dysfunction may persist for longer periods of time ranging from days to weeks following surgery and those records are lacking in the present study. Further recordings after various times postoperatively would have given us a more comprehensive picture on long term effects of the drugs on cognitive function post-operatively.

CONCLUSION:

Thus, from the data analysis of the tests we had performed, it can be concluded that alprazolam gives rise to cognitive dysfunction more than that of lorazepam but the association is not statistically significant (p-value >0.05) when tested with 2 of the 3 neuropsychometric tests done—viz. Rey's Auditory Visual Learning test (RAVLT) and Digit Span Test (DST). However, when tested by use of Trail Making Test Part A, alprazolam did affect cognitive processing speed more than tab lorazepam and the association was statistically significant. (P-value <0.05).

So, administration of either of alprazolam or lorazepam makes little difference when it comes to incidence of most modalities of post-operative cognitive dysfunction following major non-cardiac surgery of <3 hours duration under general anesthesia and age group of 30-50 years.

However there was statistically significant association between use of tab alprazolam and reduced cognitive processing speed when compared to tab lorazepam, as compared through Trail Making Test part A.

So, use of alprazolam gave rise to decreased cognitive processing speed than compared to tab lorazepam.

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Conflicts of interest:
There are no conflicts of interest.

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