Original Article

Role of Anxiolysis in Post-surgical Recovery; A Study Among Cases of Acute Appendicitis

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Objective: To evaluate the role of alprazolam, a short acting, yet potent anxiolytic and sedative of the benzodiazepine class of drugs in recovery in cases of acute appendicitis.

Methods: We conducted a prospective case-control study between September 2017 to November 2017 on patients who had undergone open or laparoscopic appendectomies at a tertiary care hospital. Participants were randomly grouped into either Group A who received oral alprazolam 0.5mg once daily for 7 days (including the post-operative hospital stay) or Group B who received no anxiolytic either post-operatively or on discharge. Data was collected via a face-to-face interview with a member of our research team who filled their respective questionnaires at time-points of discharge, and at 2, 4 and 6 weeks follow-up.

Results: A total of 73 patients studied over 3 months showed that mean anxiety levels and pain scores were decreased in the group which had been prescribed alprazolam 0.5mg for 1 week. Return to normal routine activity was also noted to be quicker in the same group

Conclusions: According to the data gathered in our study, the use of anxiolytics in post-surgical care may be justified due to faster recovery and better patient satisfaction. The adverse effects of the benzodiazepine class of drugs do not outweigh the benefits in post-surgical care.

Keywords: appendicitis, alprazolam, benzodiazepines, efficacy, appendectomy, recovery, post-operative management, Pakistan.

Introduction

The outcome of any successful surgical procedure is often measured by the time taken and patient care during the post-operative hospitalization involved. Advances in laparoscopic techniques and ERAS protocols (Enhanced Recovery After Surgery) have effectively minimized the duration of hospitalizations and decreased rates of post-operative complications in western countries.[1,2] However, in Pakistan's hospital settings there is a lack of credible evidence to support the success or failure of modern techniques to reduce post-operative hospitalizations especially for open procedures. Currently most post-operative care revolves around minimization of pain and prevention of further complications. Pain management typically follows the WHO guidelines for analgesia which were first described in 1986 for the management of cancer related pain.[3] However, the step-ladder format of pain relief has been successfully utilized for all kinds of post-operative pain.[4] However, it should be noted that often, post-operative pain relief involves the heavy use of opioid analgesics which are not without their own complications, especially with the adolescent population; leading to higher likelihood of adverse outcomes such as addiction and gastrointestinal system upsets.[5] Furthermore, hospitals with more modern protocols of pain management such as multi-modal analgesia have also mostly resorted to heavy use of opioid analgesics, though with a faster recovery time.[6] The medical community is, therefore, constantly on the search for the development of newer, more efficient protocols and techniques to reduce post-operative hospitalizations and speedier recoveries. One such method has been to use the benzodiazepine class of drugs both pre-operatively and post-operatively in order to reduce anxiety and improve sedation in hospitalized settings.[7,8]

Hospitalization is frequently associated with increases in anxiety, depression and clinical trials have shown improvement in patient outcome with their reduction before and after the operations.[9] This is especially important in procedures involving removal and/ or manipulation of organs such as arthroplasty or hysterectomies.[8,10] One study in the UK among 310 patients who had undergone coronary bypass graft surgery found that socioeconomic factors and depression among the cases had significantly delayed recovery and prolonged hospital stay.[11] Anxiety has been known to invoke a stress-hormonal response leading to release of glucocorticoids, and sympathetic stimulation,[12] thereby worsening patient recovery. A randomized controlled trial showed that patients undergoing gastric bypass surgery reported anxiety

Levels between 25% and 33% even two years after their respective surgeries.[13] The hospitalized patient is therefore at much risk of anxiety related worsened outcomes. It is a common practice among doctors use of common anxiolytics such as alprazolam both pre-operatively and post-operatively to maintain a reduced stress level among patients. In our study, we aim to quantify and evaluate the efficacy of alprazolam in the improvement of patient outcomes by observing patients during the post-operative period and on follow up.

Methods

We conducted a randomized clinical trial between September 2017 to November 2017 of patients who had undergone open or laparoscopic appendicectomies. Patients in Group A were prescribed alprazolam 0.5mg once daily for 7 days after surgery (encompassing both post-operative hospital stay as well as discharge) and patients in Group B were not prescribed any anxiolytic either during post-operative care as well as on discharge and both groups were monitored on follow-up at 2 weeks, 4 weeks and 6 weeks.

Alprazolam 0.5 mg was chosen as the anxiolytic due to its safety, cost-effectiveness and easy availability.[14,15] Parameters for effective recovery during a complete 6-week period included pain assessment via Visual analogue scale (VAS),[16] Hamilton Anxiety rating scale (HAM-A)[17] for assessment of anxiety, and a questionnaire based follow-up on the patient's return to normal routine life at 2, 4 and 6 weeks post operatively.

The data for a total of 73 participants was collected over a period of 3 months through a face-to-face interview done on the first post-operative day and at follow up time-points of 2 weeks, 4 weeks and 6 weeks. On discharge, our team recorded the pain of all recruited patients with the Visual Analog Scale (VAS) and using the HAM-A scoring questionnaire at follow up along with our own questionnaire for return to routine life activity.

The patients who did not present at follow-up were recorded as missing at time of data entry. Patients were randomly selected and placed into one of two groups, Group A being the recipients of alprazolam and Group B being the controls receiving no anxiolytic drug during post-operative phase as well as on discharge.

Results

A total of 73 participants were eligible for the study. Patients were randomly listed in either Group A or Group B. A total of 36 cases were registered in Group A, whereas 37 cases were registered in Group B. Tables 1 and 2 show the breakdown of the biodata details regarding the cases. All surgical procedures were conducted by a team which included but was not limited to a Senior Registrar, up to two Postgraduate trainees, an assisting House-Officer as well as an assisting Nurse. The Anaesthetists team included a senior Medical Officer, a Junior House Officer as well as an operation theater technician. All surgical procedures were carried out in the emergency department, and postoperatively managed in the surgical ward by a team of both senior and junior doctors as well as the nursing staff.

All patients were given opioid analgesia, that is, 3mg Nalbuphine as per post-operative protocols regarding pain relief. The doses were adjusted in either once-daily (OD), twice daily (BD) or thrice daily (TDS) as per clinical assessment. The mean duration of hospital stay was 1.4 days. For the purpose of our study, we aimed to assess recovery in both groups by measuring pain, anxiety levels as well as return to routine life (in our questionnaire). Anxiety levels were assessed by the HAM-A questionnaire filled out by our researchers at follow-up and pain scores were assessed at discharge, 2 weeks, 4 weeks and 6 weeks of follow-up. All patients discharged were advised follow-up after 2 weeks in the out-patient department. Patients were advised follow-up at 4 weeks and 6-week time-points. For practical purposes as well as to identify confounders early on, we added an additional "not-required" status for patients who could not commit to follow-up. We recorded the number of patients who were present for a follow-up as shown in **Table4 &5.**

The patients who missed one time-point of follow-up were excluded from the study. 6 patients dropped out of the study at the 4-week follow-up time-point and 10 patients dropped out of the study at the 6-week follow-up time-point. More people dropped out of the study in Group-A than Group-B.The HAM-A scores for the patients in Group A were significantly lower than those of Group B at all stages of follow-up. At the 2-week time-point, 14.93% of patients in Group B reported as having moderate to severe anxiety (HAM-A>25-30) whereas only 4.48% of the cases in Group A reported as having severe anxiety **Fig-1.**

At the 4-week time point 38.6% of all the cases in Group B reported as having mild-moderate levels of anxiety as compared to17.54% of all the cases in Group A with reports of the same levels of anxiety **(Fig-2).**

This progress correlates with the other parameters set for recovery in the participants. Patients in Group B reported a lesser degree of pain reduction as well as a slower return to normal routine activities as compared to patients in Group A, although this tapered out to near-same results 6 weeks post-surgery. Mean anxiety levels were overall lower as in Group A as compared to Group B. We attempted to exclude as many confounders as possible by excluding all patients with serious co-morbidities such as diabetes, hypertension and psychiatric illnesses. We also excluded extremes of age. Our study's results may be influenced by patient compliance since participants self-reported their drug intake. Our questionnaire did not assess any other co-morbidities that may have developed in the duration of follow-up. Gender may also be noted as a confounding factor, as no gender specific details were addressed. There were more males than females in our study according to the data collected, however, we attempted to exclude a selection bias based on gender by randomly allocating the data in our software.

Table-1: Group summary.

Group	N
Group A	36
Group B	37
Total	73

Table-2: Grouping by Gender.

Gender	N
Male	44
Female	29
Total	73

Table-3: Duration of hospitalization.

	N	Minimum	Maximum	Mean	Std. Deviation
Duration of hospital stay	73	1.00	3.00	1.4247	.55070
Valid N (list-wire)	73				

Table-4: Summary of follow-up.

Did the patient follow up after 2 weeks	Yes	N	67
	No	N	73
	Total	N	04
Did the patient follow up after 4 weeks	Yes	N	12
	No	N	09
	Not required	N	03
	Total	N	03
Did the patient follow up after 6 weeks	Yes	N	12
	No	N	09
	Not Required	N	03
	Total	N	03

Table-5: Breakdown of follow-up.

Follow-up		Group A Count	Group B Count
Did the patient follow up after 2 weeks	Yes	30	37
	No	6	0
Did the patient follow up after 4 weeks	Yes	26	31
	No	1	3
	Not required	3	3
Did the patient follow up after 6 weeks	Yes	16	19
	No	9	10
	Not Required	1	2

Table-6: Mean anxiety level comparision.

Group		HAM-A Score	HAM-A Score	HAM-A Score
Group A	Mean	1.7333	1.3846	1.3750
	N	30	26	16
	Std. Deviation	.63968	.49614	.5000
Group B	Mean	2.0541	1.8387	1.4211
	N	37	31	19
	Std. Deviation	.70498	.52261	.50726
Total	Mean	1.9104	1.6316	1.4000
	N	67	57	35
	Std. Deviation	.690447	.55522	.49705

Table-8: Return to normal routine activity (as assessed by questionnaire).

Return to normal routine			Group A	Group B
At 2 weeks post-surgery	Yes	N	20	18
	No	N	10	19
At 4 weeks post-surgery	Yes	N	24	28
	No	N	02	03
At 6 weeks post-surgery	Yes	N	16	19
	No	N	0	0

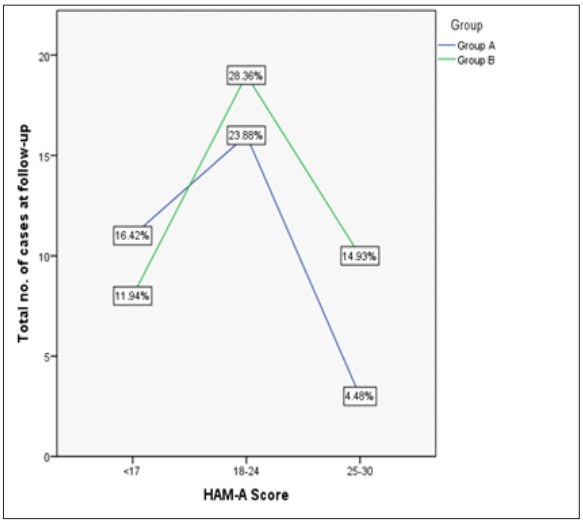

Fig-1: HAM A score at 2 weeks time-point.

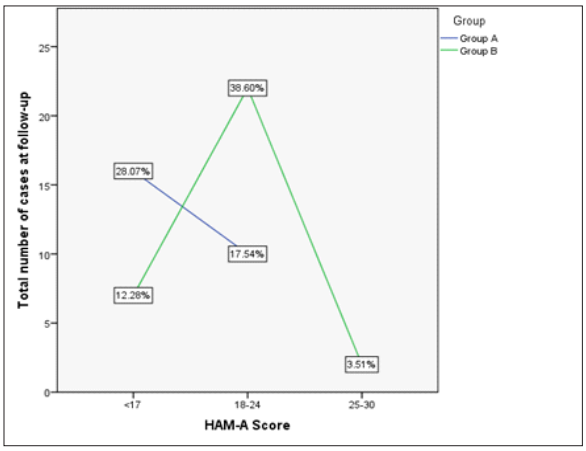

Fig-2: HAM-A score at 4 week follow up.

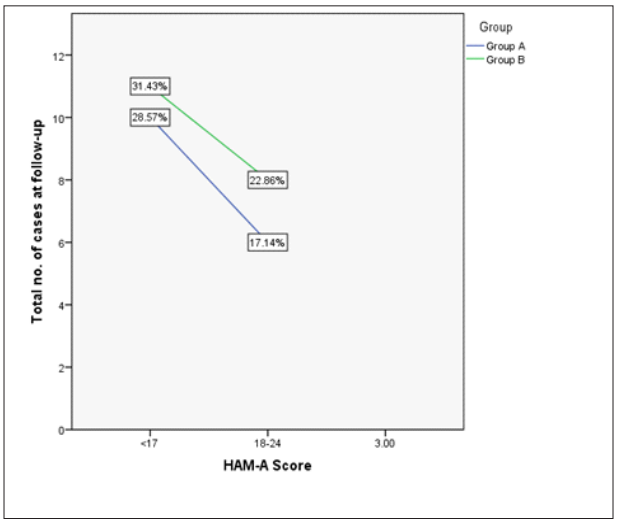

Fig-3: HAM-A score at 6 week followup.

Discussion

It has been well established that anxiety adversely affects the human body. Stress exerts a toll on nearly all of the organs with the release of endocrine hormones such as cortisol, epinephrine, norepinephrine among countless others. While these are normal responses to stress in the body, pre--surgical anxiety as well as post-surgical anxiety have also been well documented even with the best patient care facilities. Hospitalization in general is an incredibly stressful experience for people of all ages. Even more so, in our setting, that is, the government sector, patient stress is likely to be exacerbated due to both patient-centric and hospital-centric factors. While in most cases, post-operative pain is the most important cause of discomfort among patients, it is

Table-7: VAS scoring at time of discharge, 2 weeks, 4 weeks and 6 weeks follow-up.

Pain Score	Discharge		2-week follow-up		4-week follow-up		6-week follow-up	
	Group A N	Group B N	Group A N	Group B N	Group A N	Group B N	Group A N	Group B N
1	0	0	6	2	11	14	14	17
2	3	1	12	19	12	16	2	2
3	15	15	12	15	3	1	0	0
4	15	18	0	1	0	0	0	0
5	3	3	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0

Factors ranging from poor socioeconomic status to poor interpersonal skills of the health-care providers may be a source of extreme stress on the patient. Ultimately, all of this may impede patient recovery. For our study we chose the most easily available anxiolytic in our setup as well as the simplest cases to study and follow up in order to exclude as many confounding factors as possible in order to study the role of anxiolysis in post-surgical recovery. Our study shows that all of the patients given alprazolam 0.5mg for 1 week had a lower stress levels and lower complaints of pain. Only 10 patients complained of not being able to return to normal routine activities in Group A as compared to 19 in Group B. Another point worth noting may be that more patients from Group A were likely to discontinue follow-up as compared to Group B patients. In effect, our study shows that anxiolysis improves quality of life as well as inhibits delayed recovery in post-surgical cases of appendectomies. Our study shows that while almost all patients recovered fully at 6-weeks post-surgery, there was a significant difference between anxiety levels among cases and controls at the 4 weeks post-surgery. This may suggest that while almost all patients having undergone appendectomies may have the same quality of life at later stages, anxiolysis may play a significant role in patient well-being during the initial month post-surgery. Another noticeable difference is the number of drop-outs in follow-up were significantly greater in Group A than in Group B (ref. **Table 5)** especially after the first follow-up. This may suggest good recovery since the patients might not have felt the need for follow-up. We have acknowledged several confounding factors in our study and it is too early to state whether prescription of anxiolytics should be part of post-operative protocol, it may be reasonable to suggest that further, larger scale studies should be carried out to understand the efficacy of anxiolysis in post-operative care.

Conclusions

According to the data gathered in our study, the use of anxiolytics in post-surgical care may be justified due to faster recovery and better patient satisfaction. The adverse effects of the benzodiazepine class of drugs do not outweigh the benefits in post-surgical care.

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