The Study to Evaluate Intraoperative Sedative and Perioperative Analgesic Requirement of Pregabalin (75) MG in Tympanoplasty- A Randomized Controlled Study

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ABSTRACT

Background

Tympanoplastyis a surgical technique to repair a defect in the tympanic membrane with the placement of a graft. Use of opioids to control sympathetic response may lead to hypotension,postoperative respiratory depression and delayed recovery. Gabapentinoidshave anti-nociceptive effects. They reduce opioid requirement in multimodal analgesia techniques.Pregabalin is a gabapentinoid drug.It has been used in doses of50 mg,75 mg,150mg,300mg and 600mgas premedication by oral route. The effects of pregabalin have not been studied for monitored anaesthesia care in tympanoplasty. The aim of our study was to assess the efficacy ofpregabalin (75 mg) administered as oral premedication to reduce intraoperative sedative andanalgesic requirementandside effects in patients undergoing tympanoplasty under monitored anaesthesia care.

Methods

Sixty patientswere randomly selected to receive either pregabalin (in Group A) 75 mg tablet or similar looking controlled drug i.e., B complex (inGroup B),as oralpremedicationone hour before surgery.Injection midazolam intravenous bolus was given followed by infusion. Patient having Numerical Rating Scale(NRS)≥4 or complaint of pain,injection fentanyl was used as rescue analgesic. Postoperatively time to request first analgesic was noted.

Inclusion Criteria

American Society of Anesthesiologists (ASA) physical status I–II patients of 18-60 years of age.

Exclusion Criteria

Allergic to study drug, Pregnancy, Patient refusal.

Results
The total midazolam consumption inB complex Groupwas 3.25 ± 0.33 mgand3.04 ± 0.38 mginpregabalinGroup, p=0.03.The total fentanyl consumption inB complex groupwas 76.67± 15.82 mcgandin pregabalingroup itwas 35.33 ± 8.6 mcgp=0.000, Time to first request of analgesic was354 ± 63 mins in B complex groupand444 ± 64mins inpregabalingroup.
Conclusion
Premedication with pregabalin75mgsignificantly reduced the requirement of fentanyl and midazolamduring monitored anaesthesia carefor tympanoplasty.It significantly prolonged postoperativeanalgesia durationand reduced postoperative analgesic requirement.

Keywords: Midazolam, Monitored Anaesthesia Care,NRS Score.
DOI Number: 10.48047/nq.2025.23.1.NQ25003 **NeuroQuantology 2025; 23(1):22-29**

INTRODUCTION

Tympanoplasty[2]is a surgical technique to repair a defect in the tympanic membrane with the placement of a graft.The goal of this surgical procedure is not only to close the perforation but also to improve hearing. Handling of middle ear cavity produces stress response. Harvesting graft and cartilagecauses painful stimuli, therefore continuous sedation and analgesia is required to keep the patient stress free and immobile.

Analgesia is an important modality in anaesthesia. Good pain control avoid stress response and reduces requirement of anaesthetic agents. It keeps stable haemodynamic response. Perioperative pain may also amplify the surgical stress response which could have deleterious effects on the postoperative recovery. Control of the sympathetic response often requires high doses opioids, they can also lead to postoperative respiratory depression and delayed recovery. Post-operative nausea vomiting is another common undesirable side effect of opioids. High doses of opioids and anaesthetics can lead to hypotension.

Pregabalinis a gabapentinoid drug and acts by inhibiting calcium channels. Gabapentinoidsareanti-convulsantswith membrane stabilizing and anti-nociceptive effects. These drugs act on presynaptic α2–δ subunit of voltage-dependent calcium channel. The anti-nociceptive effect is due tothe reduction of theCa^{2+}influx atpresynaptic terminalsinhyperexcitedneurones(ref). There isreduction in the release of several excitatoryneurotransmitters likesubstance P, calcitoningene-related peptide, norepinephrine and glutamate. Hence there is dampening effect on the hyperexcitability of dorsal horn neurones induced by tissue injury.

Pregabalin was approved for medical use in the United States in 2004. It was developed assuperior to gabapentin. It is used in anxiety disorder, seizures, chronicpain,alcohol withdrawal syndrome.Different doses ranging from 50 - 600mghave been used.[3,4,6,7,8]

Premedication with pregabalin has been found to decrease postoperative pain and reduce opioid consumption in patients undergoing major surgeries. It works by decreasing the number of pain signals that are sent out by damaged nerves in the body.Goodpain control with less opioid consumption with use of these drugs can benefit these patients by reducing postoperative nausea and vomiting (PONV). Previously, gabapentin has been studied in patients undergoing ear-nose-throat (ENT) surgery under monitored anaesthesia care. Higher dose of Gabapentin (1200 mg) was effective in reducing analgesic requirement but was associated with dizziness in large number of patients.[3]Lower dose of gabapentin (600 mg) was found to reduce perioperative analgesic requirement without side effects.[4].

The effects of pregabalin have not been studied for monitored anaesthesia care in ambulatory tympanoplasty. The aim of our studywas to evaluate the efficacy of oral pregabalin(75mg) administered as premedication to reduce intraoperative sedative and postoperative analgesic requirementin monitored anaesthesia care for tympanoplasty.

AIM: The aim of our study was to evaluate the efficacy of oral pregabalin administered as premedication to reduce intraoperative sedative and postoperative analgesic requirement in monitored anaesthesia care for tympanoplasty.

OBJECTIVE

1. Evaluation of requirement of intraoperative fentanyl and midazolam in both groups A and B
2. To determine time to first analgesic requirement postoperatively in both groups A and B
3. To evaluate the haemodynamic changes of pregabalin.[1]
4. To know side effects of pregabalin

METHODSAND MATERIAL

This wasa randomized, double-blind clinical studyconducted at Krishna Institute of Medical Sciences in Karad, Maharashtra.Randomization were performed according to computer-generated random numbers contained in sealed envelopes.

Inclusion Criteria

After obtaining the approval of the Institutional Ethics Committee and written informed consent from the patients, American Society of Anaesthesiologists (ASA) physical status I–II patients in the age group of 18-60 years undergoing tympanoplasty under monitored anaesthesia care were included for the study.

Exclusion Criteria

The criteria for exclusion were allergic history to the drug, contraindication to the use of any of the drugs in the study, reactive airway disease,renal disorder, history of peptic ulcer, bleeding diathesis, pregnancy,history of psychiatric medications and patient refusal.

Sixty patients posted for tympanoplasty under monitored anaesthesia carewere randomly selected to receive either pregabalin75 mg,labelled as drug A or thesimilar looking controlled drug, B complex tablet,labelled as drug B,1 hr before surgery as oral premedication.The data collectors and data analysers were blinded to the study. After obtaining written informed consent by the patient the drug was administered bya preoperative roomnurse who was notinvolved in the study. In the operating room, themonitors for pulse oximetry, electrocardiogram(ECG), noninvasive blood pressue(NIBP), respiratory rate (RR), end tidal carbondioxide(EtCO2)were attached. Patients were explained about the numerical rating scale (NRS) that is from a score of0 (no pain) to10(worst possible pain). All patients wereadministeredmidazolam 1mg, fentanyl 0.5 µg/kg intravenously and local anaesthesia lignocaine -adrenaline 2% at the site.

Ear ring Block for Tympanoplasty[5]

LA injection of approximately volume of10-12 mlis injected in the postauricular region in posterior,superior inferior meatal walls, in the front of the helix crusto block auriculotemporal nerve and then at thesite of endaural incision at the incisura. The medial surface of the tragus. The external meatus is opened and injected superiorly in the bone meatus at the 12 O'clock position, posteriorly, inferiorly at the 6 O'clock positionand anteriorly. Injecting the posterior and inferior ear-canal skin anesthetizes the auricular branch of the vagus nerve. The ME mucosa is anesthetized by trickling of the AS through tympanic membrane (TM) perforation.

OT anaesthetist who was blind to the randomization was started sedation with continuous infusion of an i.vof midazolam 0.03 mg/kg/hr. Sedation level was assessed according to Ramsay sedation scale and midazolam infusion wastitrated accordingly. Intraoperative pain was assessed by numerical rating scale (NRS) score. The patients was evaluated pain score using NRSat interval of 5,10, 20.10 min interval intraoperatively till the procedure end. Patient having NRS≥4 or complaint of pain will giveni.v bolus of fentanyl (0.5 µg/kg).The total amount of fentanyl consumption was noted and recorded. The first analgesic request was regarded as the time when administration of an additional analgesic that was given in the postoperative period as per demand within 24 hours postoperatively.Patients were questioned at 30 min,1hr, 2,4,6,8, 12, 16,20,24 hr post operatively about any side effect, PONV and dizziness. If nausea and vomiting occurred, ondansetron 4 mg i.v was given. PONV and dizziness is very commom side effectsin tympanoplasty postoperatively because vestibular apparatus pressure effect by membrane repair patch and ear dressing.

A power analysis suggested sample size to be 30 patients per group to detect a 40% reduction in analgesic consumption. The power of 80% was applied. Student's pair *t*-test and fisher test was used to analyze data. $P<0.05$ is defined as significant.

RESULTS

This randomized controlled double blindsingle centre study was conducted in aKIMSDU, Karad over a period of 6 months from April 2021 to August2021.

After obtaining the approval of the Institutional Ethics Committee (Ref.no. KIMSDU/IEC/05/2021) a total of 60 patients, posted for elective surgery for tympanoplastywere recruited to the study after screening for inclusion and exclusion criteria. Both groups were comparable with respect to the demographicand operational factors. No significant differences were found among them with respect to age, sex, weight, duration of surgery. Table 1.

The total midazolam consumption was 3.25 ± 0.33mg in the group B and3.04 ± 0.38mg in thegroup A,The difference in the means was statistically significant (p=0.03), (Table 2, Fig 1) The total fentanyl consumption was 76.67 ± 15.82 mcg ingroup B and35.33 ± 8.6 mcg ingroup A, p=0.000(Table 2, Fig 2). The time to first request analgesic was 354±60 mins ingroup B and444±60 mins in group A (Table 2, Fig3)

67% patients had nausea in groupB and27% in Group A, 27% patients had dizziness in Group B and 33% patients had dizziness inGroup A (Table 5)

Intra operatively 90 % patients had pain score ≥4 in Group B and 83% patients had pain score <4 inGroupA,10% patients had pain score<4 in Group B and 17% patients had pain score ≥4 in Group A(Table 3)

Sedation score 2 was maintained in 67% patients ingroup Band10% in group A. 33% patients had maintainedsedation score 3 ingroup B andit was in 90 % patients in Group A(Table 4)Highest HR in Control group Bwas95/minand 86 /min in Group A. Lowest HR in control group B was 70/min and 69/min in Group A(Table 6). Highest MAP in groupB was 110 mm of hg and102 mm of hg in Group A. Lowest MAP in group B was 71 mm of hgand65 mm of hg in study A (Table7)

Variable	Group A	Group B
Age(years)	33.66 ± 11.31	34.23 ± 10.00
Sex male: female	16:14	13:17
Body weight(kg)	55.76 ± 8.29	57.46 ± 8.44
Duration of surgery(min)	110.5 ± 12.75	114.3 ± 12.36

Table 1: Demographic variable

Variable	Group A	Group B	p value
Total midazolam Consumption (mg)	3.04 ± 0.38	3.25 ± 0.33	0.03
Total fentanyl Consumption (mcg)	35.33 ± 8.6	76.67 ± 15.82	0.000
Time to first request analgesic (mins)	444 ± 60	354 ± 60	0.000

Table 2: Total midazolam, fentanyl, paracetamol and time to first request analgesic

	Group A	Group B	P value
Intraop pain score	≥ 4 5(17%)	27(90%)	0.00001
	< 4 25(83%)	3(10%)	

Table 3: Inraop pain score in both groups

	Group A	**Group B**	**P value**
Sedation score	23(10%)	20(67%)	0.00001
	327(90%)	10(33%)	

Table 4: Intraop sedation score in both groups

Side effect	**Group A**	**Group B**	**P value**
Nausea	8(27%)	20(67%)	0.001
Dizziness	10(33%)	8(27%)	0.4

Table 5: Side effects in both groups

Heart Rate	**Group A**	**Group B**	**P value**
Highest HR in min	86	95	0.005
Lowest HR in min	69	70	

Table 6: Highest HR and lowest HR in both groups

Mean Arterial Pressure	**Group A**	**Group B**	**P value**
Highest MAP in mm of hg	102	110	0.0034
Lowest MAP in mm of hg	65	71	

Table 7: Highest and lowest MAP in both groups

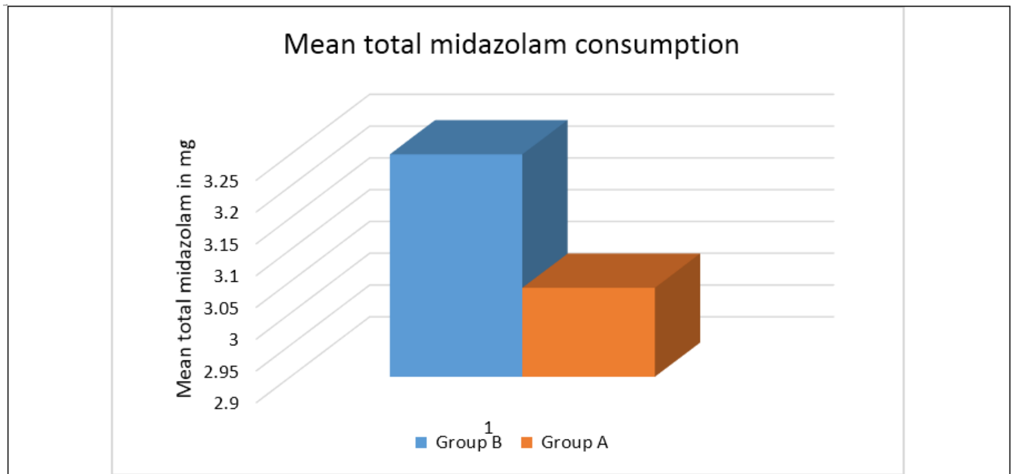

Figure 1: Mean total midazolam consumption in both groups

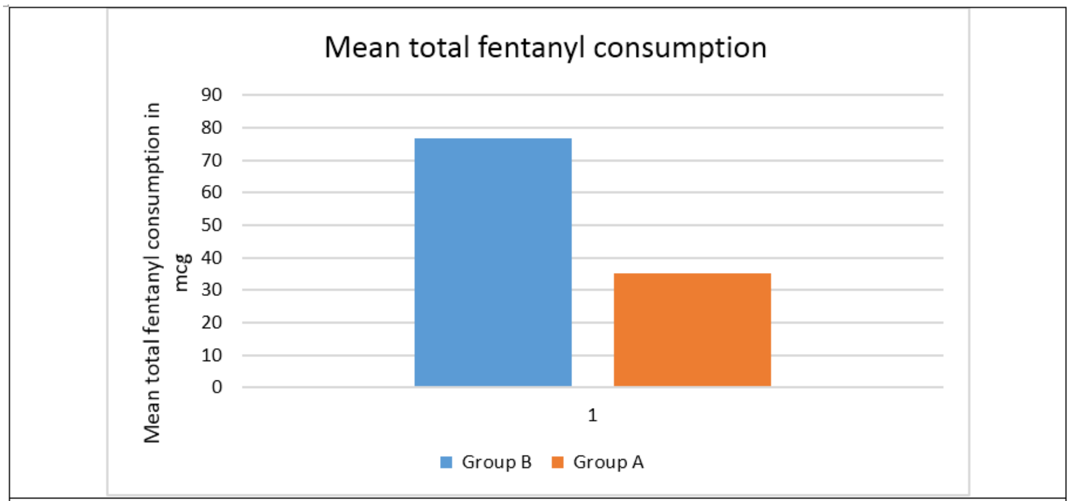

Figure 2: Mean total fentanyl consumption in both groups

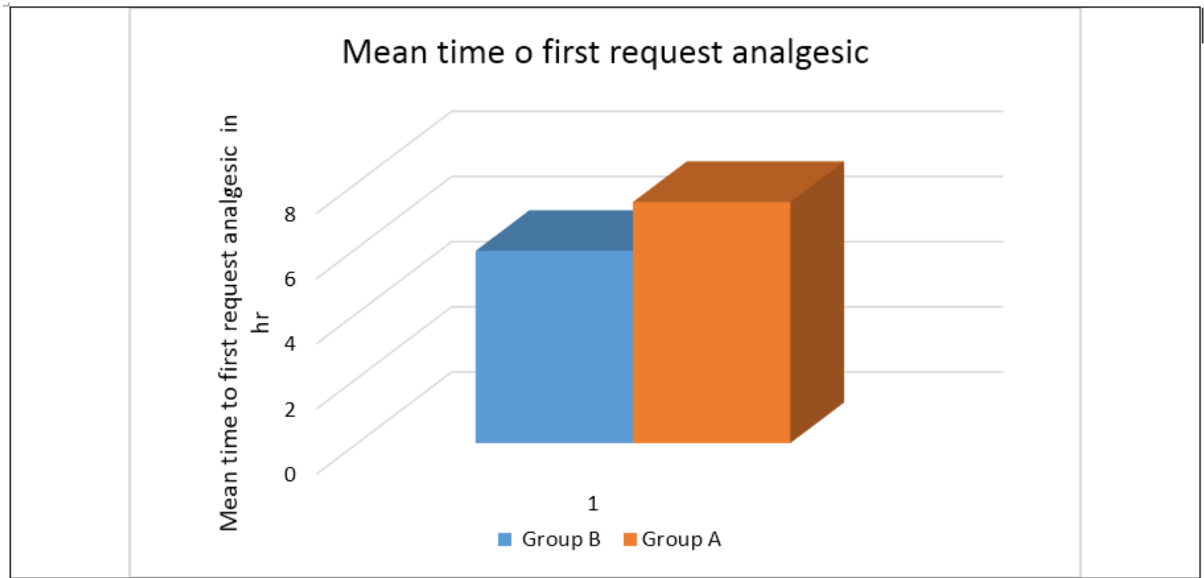

Figure 3: Mean time to first request analgesic in both groups

DISCUSSION

There are veryfew studies regarding theuse of pregabalin in monitored anaesthesia care for tympanoplasty. The aim of our study was to assess the efficacy of pregabalin (75 mg) administered as oral premedication to reduce intraoperative sedative andanalgesic requirementandside effects in patients undergoing tympanoplasty under monitored anaesthesia care.

Use of higher doses of pregabalinshowed good analgesic and sedative property but more prone to adverse effect.Lower dose of pregabalin 50 mg reduces pain but not opiod consumption and higher doses of pregabalin 150 leads to adverse effect. Postoperative analgesic consumption was significantly less with pregabalin.[3,4]

The Perioperative administration of pregabalin 75 mg provided limited analgesic benefit in the postoperative period in patients undergoing laparoscopic cholestectomy.[6]

Kochharet al studied the efficacy of pregabalin in septoplasty undermonitored anaesthesia care. Premedication with pregabalin (150 mg) reduced intraoperative sedative and perioperative analgesic requirement with tolerable side effects.[7]

In our studythe total midazolam(3.04 ± 0.38 mgversus 3.25 ± 0.33 mg,p=0.0034) and fentanyl consumption (35.33 ± 8.6 mcgversus 76.67 ± 15.82 mcg, p=0.000)was significantly less in patients receiving 75 mg pregabalin as oral premedication.Time to first request for analgesic was also significantly prolonged in the Group A(444 ± 60 minsversus 354± 60 mins ingroup B,p=0.000).

Analgesia was better after premedication with pregabalin 150mg than after diazepam 5 mg, both with ibuprofen 800 mg in day-case gynaecological laparoscopic surgery. However in contrast to our findings in this study,pregabalin 150 mg did not prolong the post-operative analgesia time and reduce the amount of postoperative analgesics required.[8]However it is reported that the need for postoperative analgesia was lessin patients who were given pregabalin 150 mg as premedication at 2 hours postoperatively as compared to those patients administered placebo.[9]

It is reported that the administration of 300 mg pregabalin prior to tonsillectomy decreases fentanyl consumption without increasing the incidence of adverse effects compared with 4 mg diazepam.[10] In our study the total fentanyl consumption in groupB was 76.67 ± 15.82 mcg and it was 35.33 ± 8.6 mcg ingroup A, p=0.000.

Preoperative pregabalin administration (75-300 mg) increased perioperative sedation in a dose-related fashion, but failed to reduce preoperative state anxiety, postoperative pain, or to improve the recovery process after minor elective surgery procedures.[11] Our study showed, Sedation score 2 was maintained in 33% patients inGroup Band5% inGroup A. 17% Patients maintainedsedation score 3 in Group B andit was in 45 % patients in Group A. Administration of pregabalin600mg, divided in two preoperative doses, significantly reduced postoperative pain as well as morphine consumption in patients undergoing laparoscopic cholecystectomy withincreased incidence of dizziness.[12]Similarly

Inour study the incidence of dizziness was 17% more in the Group A.Preoperative pregabalin is associated with significant reduction of PONV and should not only be considered as part of a multimodal approach to postoperative analgesia but also for prevention of PONV.[13]In this study we observed 20% reduction in nausea and vomiting withthe administration of Drug A. PONVand dizziness are commom in ear surgeries because of the proximity ofvestibular apparatus.

Premedication with oral pregabalin 75 mg and 150mg for attenuation of haemodynamicpressor response to airway instrumentation during general anaesthesiafor various procedures was studied by Rastogi,[14]the study concluded that pregabalinin a dose of 150 mg as oral premedication was effective in attenuating the haemodynamic response to orotracheal intubation. It could be seen in their study that even a dose of 75 mg supressed the pressor response.In our study, Drug A supressed hemodynamic response to airway instrumentation. The mean highest heart rate response (p=0.005) and the mean highest MAP responseweresignificantly less in the patients given pregabalin premedication (p=0.0034).

STRENGTHS OF STUDY

To the best of our knowledge, this is first study of using midazolam infusion intraoperatively for monitored anaesthesia care in tympanoplasty surgery in a randomized controlled double blind study. Most of the studies in literature pertain to the using propofol infusion for monitored anaesthesia.

LIMITATION OF STUDY

We haven’t study ambulatory period postoperatively

We didn't mention placebo effect postoperatively

SUMMARY AND CONCLUSION

In tympanoplsty under MAC

1. Pregabalinsignificantly reduced the requirement of fentanyl intraoperatively.
2. Pregabalinsignificantly reduced postop analgesic requirement.
3. Time to first request analgesic requirement in low in pregabalin received group.

CONCLUSION

Premedication with pregabalin 75mg significantly reduced the requirement of fentanyl and midazolam intraoperatively as part of monitored anaesthesia care during surgery for tympanoplasty.It significantly prolonged postoperative analgesia duration and analgesic requirement.

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