Revista da Sociedade Portuguesa de Anestesiologia
http://revistas.rcaap.pt/anestesiologia
https://dx.doi.org/10.25751/rspa.26144

ARTIGO ORIGINAL

Comparison of Prophylactic Ondansetron and Pregabalin for Postoperative Nausea and Vomiting: A Randomized Controlled Study

Comparação da Administração Profilática de Ondansetron e Pregabalina para Náuseas e Vómitos Pós-operatórios: Estudo Controlado Randomizado

Uzma Raihan[1], Prakash Dubey[1]

Afiliações
[1] Department of Anesthesiology and Critical Care Medicine, Indira Gandhi Institute of Medical Sciences, Patna, India.

Keywords
Postoperative Nausea and Vomiting/drug therapy; Postoperative Nausea and Vomiting/prevention & control; Ondansetron; Pregabalin
Palavras-chave
Náusea e Vómito Pós-Operatórios/prevenção e controlo; Náusea e Vómito Pós-Operatórios/tratamento farmacológico; Ondansetron; Pregabalina

ABSTRACT

Introduction: Pregabalin is an antiepileptic drug with antiemetic properties. We evaluated prophylactic oral pregabalin as compared with ondansetron for postoperative nausea and vomiting (PONV) in patients undergoing mastoid surgery in a randomized double-blind study.

Material and Methods: Two hundred patients of ASA physical status I and II, scheduled to undergo mastoid surgery, were randomly assigned into two groups to receive 150 mg pregabalin or 8 mg ondansetron one hour before surgery. Standard anaesthesia technique was used in all patients. Episodes of PONV were recorded during the first 24 hours for two time periods: 0–2 and 2–24 hours. Data regarding adverse effects, such as dizziness, headache and drowsiness, were also collected. Categorical variables were expressed as frequency (%) and chi-square test was applied to test the significance of association between groups and variables. Continuous variables were expressed as Mean with 95% confidence intervals. T-test was performed to compare the mean of variables between two groups. Kaplan-Meier survival analysis was performed for comparing mean or median time of events. Log-rank test was used to test the median survival time. Kolmogorov-Smirnov test was used for testing the equality of the distribution function of sedative score at each time point.

Results: Pregabalin prophylaxis in patients undergoing mastoid surgery delays the onset and decreases the episodes of vomiting within 2-hours of surgery as compared to ondansetron 8mg. It also reduces the incidence of nausea in the postoperative period, albeit at the cost of higher incidence of sedation.

Conclusion: Pregabalin effectively suppresses PONV in mastoid surgery.

Autor Correspondente/Corresponding Author*:
Prakash K. Dubey
Morada: E ¾, IGIMS Campus, Patna 800014, India.
E-mail: pkdubey@hotmail.com

RESUMO

Introdução: A pregabalina é um fármaco antiepilético com propriedades antieméticas. Neste estudo randomizado duplamente cego, avaliamos a administração profilática de pregabalina oral *versus* ondansetron para náuseas e vómitos pós-operatórios (PONV) em doentes submetidos a cirurgia mastóidea.

Material e Métodos: Duzentos doentes, estado físico ASA (American Society of Anesthesiology) I e II, propostos para cirurgia mastóidea, foram randomizados em dois grupos, para administração de 150 mg pregabalina ou 8 mg de ondansetron, uma hora prévia à cirurgia. Todos os doentes foram submetidos a técnica anestésica protocolada. Os episódios de PONV foram registados nas primeiras 24 horas em dois períodos: 0-2 e 2-24 horas. Foram igualmente registados dados relativos a efeitos adversos como tonturas, cefaleias e sedação.

As variáveis categóricas foram expressas em frequência (%) e o teste de qui-quadrado foi aplicado para testar a significância da associação entre os grupos e variáveis. As variáveis contínuas foram expressas em média com intervalos de confiança de 95%. O teste T foi aplicado para comparar a média das variáveis entre dois grupos. A análise de sobrevida de Kaplan-Meier foi aplicada para comparar a média ou mediana do tempo dos eventos. O teste de *log-rank* foi usado para testar o tempo médio de sobrevida. O teste de Kolmogorov-Smirnov foi usado para testar a igualdade da distribuição do score sedativo em cada período de tempo.

Resultados: A profilaxia com pregabalina em doentes submetidos a cirurgia mastóidea, atrasa o aparecimento e diminui os episódios de vómitos no período de 2 horas após cirurgia quando comparado com ondansetron 8 mg. A incidência de náuseas no pós-operatório também foi reduzida mas verificou-se aumento da incidência de sedação.

Conclusão: A pregabalina revelou-se eficaz na profilaxia de PONV na cirurgia mastóidea.

INTRODUCTION

Postoperative nausea and vomiting (PONV) can occur in up to 80% of high risk patients causing distress to the patient apart from increasing healthcare cost.[1] PONV contributes to complications like increased pain, bleeding, dehydration, electrolyte imbalance, delayed wound healing and may lead to aspiration.[2] Middle ear surgeries like tympanoplasty and mastoidectomy disturb the vestibular system and are associated with high incidence of PONV that is further aggravated by use of opioids.[3] The contributing factors may be the involvement of multiple types of receptors and factors like disturbances in the inner ear from surgical stimulation.

Ondansetron is a commonly used 5-HT3 receptor antagonist in PONV management. Although it is quite effective in preventing PONV following middle ear surgeries, many patients still experience PONV.[3] Hence there is need to study alternatives or combinations of antiemetics to understand the most effective.[4] Pregabalin, a compound related in structure and mechanism to gabapentin, possess anticonvulsant and analgesic properties. A meta-analysis showed that preoperative pregabalin significantly reduced PONV and rescue antiemetic administration within the first 24 hours of surgery compared with the control.[5] Although the exact mechanism of action of pregabalin is not well understood, it has been recommended for prevention of PONV, particularly in perioperative ERAS protocols that promote early patient mobilization and discharge home.[5]

The purpose of this prospective study was to compare the efficacy of prophylactic oral administration of ondansetron and pregabalin in controlling PONV in patients undergoing mastoid surgery. Any adverse effect arising out of these interventions was also noted.

METHODS

ETHICS STATEMENT

This study received ethical approval [478/IEC/2018/IGIMS] from institutional ethics committee, Indira Gandhi Institute of Medical Sciences, Patna, India on August 9, 2018 and was subsequently registered with Clinical Trials Registry - India (www.ctri.nic.in) vide registration number CTRI/2018/09/015779. Written informed consent was obtained from all the participants before enrolling them in the study. This study was conducted in accordance with the amended Declaration of Helsinki. This was a parallel group, non-inferiority, randomized, double-blind clinical trial conducted between October 2018 and August 2020 at a tertiary care university hospital.

The eligibility criteria for participants included ASA physical status 1 and 2, between 18 - 60 years of age of either sex, willing to participate and scheduled to undergo mastoid surgery in whom antiemetic was routinely indicated.

Patients who refused to participate, with known sensitivity to ondansetron or pregabalin, and on concomitant antiemetic medication were excluded from the study.

After enrolment in the study, by use of computer generated random numbers using coded numbered, opaque, sealed envelope, patients were allocated to one of two groups. Patients in group O received ondansetron 8 mg orally with sips of water one hour before induction of anaesthesia. Group P patients were administered 150 mg pregabalin orally with sips of water one hour before induction of anaesthesia.

No other premedication was administered before induction of anaesthesia. A suitable intravenous access was established after placing the routine monitors (i.e., lead II electrocardiogram, noninvasive blood pressure, and pulse oximeter). Anaesthetic induction was done with propofol 1-2 mg/kg after administering fentanyl 2 µg/kg. Tracheal intubation was facilitated with vecuronium 0.1 mg/kg and general anaesthesia was maintained with sevoflurane (2%-4%). The anesthesia technique was the same for all the patients. At the end of the procedure, the neuromuscular blockade was antagonized using a combination of neostigmine and glycopyrrolate. All patients received diclofenac 1 mg/kg every 8 hourly for postoperative analgesia as per our standard protocol. No opioid was administered during the postoperative period. The rescue antiemetic, metoclopramide 10 mg, was to be administered for severe nausea or two emetic episodes, or upon a request from the patient. If PONV persisted after metoclopramide administration, ondansetron 4 mg was to be given.[1]

The number of rescue antiemetic drugs were recorded. Demographic data and Apfel's risk score for PONV[6] were recorded for each patient. Episodes of PONV (nausea, retching or vomiting) were recorded during the first 24 hours for two time periods: 0–2 and 2–24 hours. Nausea was defined as a subjectively disagreeable sensation accompanying the urge to vomit, retching was defined as rhythmic and spastic contractions of the respiratory muscles without ejecting gastric contents, and vomiting was defined as the forceful ejection of gastric contents from the mouth.[7]

Data regarding adverse effects, such as dizziness, headache and drowsiness, were also collected. Postoperative sedation scores were evaluated using the following scale: 0 = awake, 1 = mild sedation, 2 = sleepy *but* arousable, and 3 = very sleepy.[8]

The primary outcome of this study was any nausea, emetic episodes (retching or vomiting), or both (i.e., postoperative nausea and vomiting) during the first 24 postoperative hours. The secondary outcome was any adverse effect related to the drugs used such as dizziness, headache and drowsiness.

Considering the incidence of nausea, vomiting or any other side effects after the intervention over the period of 24 hours observation, we assumed a relative risk reduction of both nausea and vomiting of around 40% or the absolute risk reduction of 20% in test group compared to control group.[6]

We expect that in control group the incidence of PONV is 30%. At 5% level of significance i.e. α=0.05 and power of the test i.e. 1-β = 80%, nearly 200 patients were to be recruited satisfying inclusion criteria i.e. 100 subjects in each group.

Block randomization method was used to allocate recruited subjects into two groups. Twenty blocks, each of size 10, was used for random allocation based on the computer-generated random number sequence taking odd numbers for pregabalin group and even random number for ondansetron group.

Group allocation and administration of medications were performed by clinicians who did not participate in data collection. The patients, care providers and those assessed were blinded to the allocated group.

STATISTICAL ANALYSIS

All statistical analyses were performed using statistical software Stata version 12 (Stata Corp, USA). Categorical variables were expressed as frequency (%) and chi-square test was applied to test the significance of association between groups and variables. Continuous variables were expressed as Mean with 95% confidence intervals. T-test was performed to compare the mean of variables between two groups.

Kaplan-Meier survival analysis was performed for comparing mean or median time of events such PONV (occurrence of nausea and vomiting analysed separately) at 2 hours and 2-24 hours respectively. Log-rank test was used to test the median survival time. Kolmogorov-Smirnov test was used for testing the equality of the distribution function of sedative score at each time point. Repeated measure analysis of variance was performed to test the sedation score at different hours at 2, 4, 6, 8 and 24 hours for group and time separately and as interaction effect of group and time.

RESULTS

Two hundred patients were recruited for the study. There were no dropouts and the data of all of them was analysed.

All the socio-demographic and clinical characteristics of the patients in both groups were comparable after the randomization showing similar distributions of all the variables in two groups (Table 1). Incidence of vomiting within two hours of surgery was significantly lower among Group P patients (p=0.009). Incidence of nausea was non-significant between two groups up to 24-hours.

No incidence of vomiting was reported in either groups during 2 to 24-hours period. Table 2 presents the comparison of time to events i.e. PONV. The number of occurrence of nausea within two hours of surgery among patients in group P was lower as compared to the patients in group O. Also, the mean time of occurrence of nausea within 2-hours of surgery among patients in group P was observed early as compared to the patients in group O. Fig. 2 presents the comparison of overall survival probabilities of occurrence of nausea

Table 1. Baseline socio-demographic and clinical characteristics between two groups

Characteristics		Group P (n=100)	Group O (n=100)	*p*-value
1. Gender	Male	56	61	0.473*
	Female	44	39	
2. Age (in years)	Mean	29.65	27.55	0.118**
	95% CI	(27.62 – 31.67)	(25.83 – 29.27)	
3. Weight (in kg)	Mean	58.47	57.95	0.7096**
	95% CI	(56.40 – 60.53)	(56.10 – 59.79)	
4. ASA	1	90	90	1.00*
	2	10	10	
5. Smoking	Yes	10	19	0.071*
	No	90	81	
6. History of PONV	Yes	1	1	1.00*
	No	99	99	
7. Motion Sickness	Yes	11	11	1.00*
	No	89	89	

Legend:
*Chi-square Test, **T-test for difference of means

Table 2. Comparison of time to events PONV between two groups

Occurrence of PONV	Group P Mean (95%CI)	Group O Mean (95%CI)	Chi-square[a]	*p*-value
Nausea within 2-hours	8/100	10/100	0.267 at 1 d.f.	0.606
	58.75 (30.86-86.64)	68.50 (45.12-91.87)		
Vomiting within 2-hours	6/100	18/100	5.360 at 1 d.f.	0.021
	46.66 (12.56-80.77)	14.44 (10.49-18.39)		
Nausea within 2-24 hours	2/100	5/100	1.847 at 1 d.f.	0.174
	375.00 (228.00 – 522.00)	220.00 (105.71-334.287)		

Legend:
[a] Log-rank test Chi-square

Table 3. Comparative sedative scores between two groups at various time points

Group/Time	Group P (n=100) Mean (95%CI)	Group O (n=100) Mean (95%CI)	Combined K-S Stat*	Exact *p*-value
2-Hours	2.56 (2.46-2.65)	1.02(0.93 – 1.11)	0.7900	0.0001
4-Hours	1.72 (1.63-1.81)	0.25 (0.157-0.34)	0.7200	0.0001
6-Hours	0.89 (0.79-0.98)	0.03 (0-0.12)	0.6900	0.0001
8-Hours	0.24 (0.15-0.33)	0	0.2100	0.024
24-Hours	0	0	NA	NA

Legend:
*Kolmogorov-Smirnov test for equality of distribution functions

between two groups indicating no statistically significant difference i.e. almost similar mean time of occurrence of nausea within 2-hours of surgery among the patients in both group. The number of occurrence of vomiting within 2-hours of surgery among patients in group P was lower as compared to the patients in group O. Also, the mean time of occurrence of vomiting within 2-hours of surgery among patients in group P was later as compared to the patients in group O. Fig. 3 presents the comparison of overall survival probabilities of

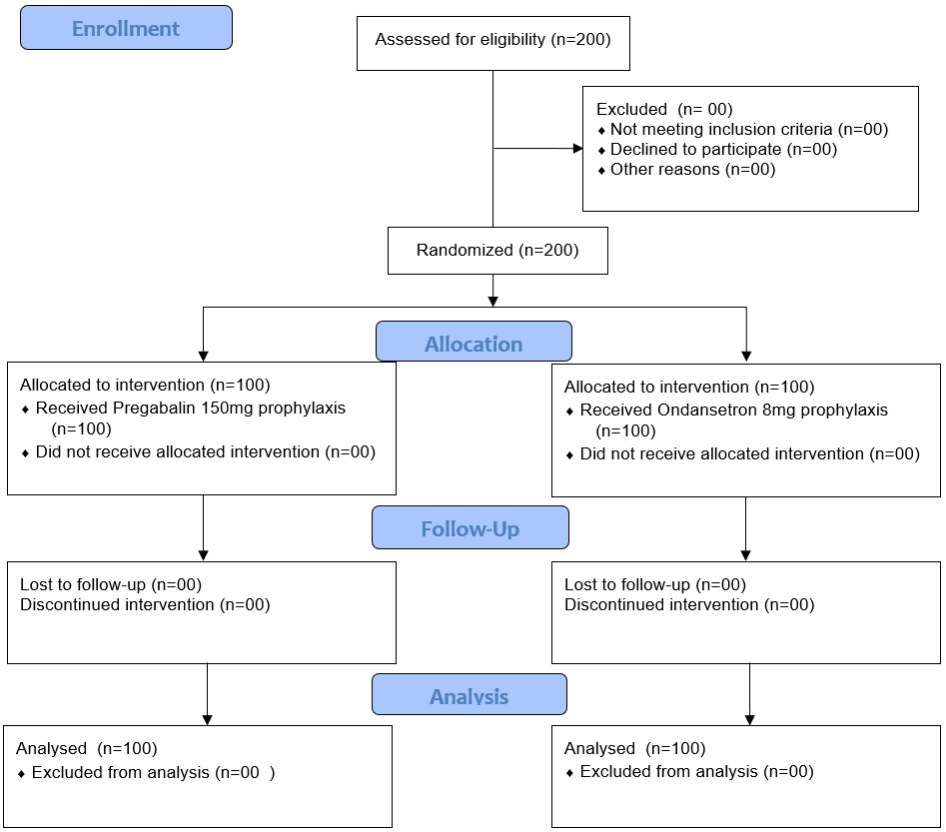

Figure 1. Consolidated Standards of Reporting Trials flow diagram of participants through the study

occurrence of vomiting between two groups indicating that mean time of occurrence of vomiting within two hours of surgery among the patients in group P is significantly higher as compared to group O. The number of occurrence of nausea within 2-24 hours of surgery among patients in group P was lower as compared to the patients in group O.

The mean time of occurrence of nausea within 2-24 hours of surgery among patients in group P was later as compared to the patients in group O. Fig. 4 presents the comparison of overall survival probabilities of occurrence of nausea between two groups indicating no statistically significant difference within 2-24 hours. Table 3 presents the comparative sedative scores between two groups at various time points.

The sedative score at each point of time was significantly higher among the patients of group P as compared to the group O. The mean sedative score within each group significantly decreased over time in both group. We did not observe any sedative signs in both groups at 24 hours. Requirement of rescue medication within 2-hours of surgery was significantly (p=0.023) lower in group P (14%) as compared to group O (27%).

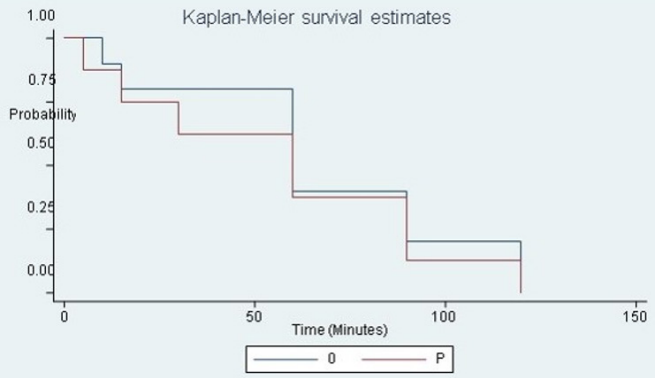

Figure 2. Comparison of overall survival probabilities of occurrence of nausea between two groups within two hours

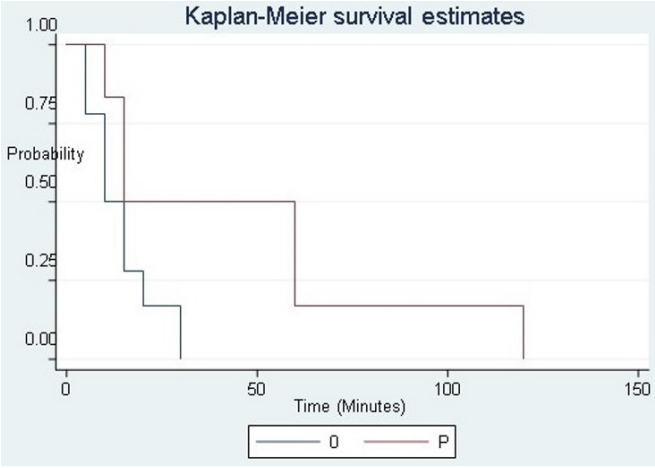

Figure 3. Comparison of overall survival probabilities of occurrence of vomiting between two groups within two hours

DISCUSSION

The main findings of this study are; Mean time of occurrence of vomiting within 2-hours of surgery among the patients in pregabalin group was significantly higher while the number of occurrence of vomiting was lower. The requirement of

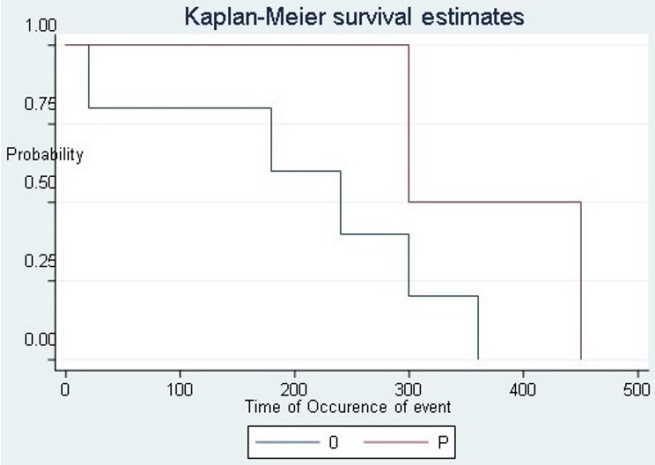

Figure 4. Comparison of overall survival probabilities of occurrence of nausea between two groups within 2-24 hours

rescue medication was significantly lower in this group.

Gabapentinoids have attracted attention for prevention of PONV as they also reduce postoperative opioid requirements and treat pain, adhering to a multimodal therapeutic approach supported among numerous perioperative ERAS guidelines.[8]

Pregabalin's antiemetic effects are likely mediated through α2/δ subunits of voltage-sensitive calcium channels, which result in multiple downstream effects depending on the associated signalling pathway.[9] Studies have shown that gabapentinoids may pre-empt nausea and vomiting through inhibition in the area postrema, decreased tachykinin neurotransmission, or reduction in postoperative inflammation.[10-12]

It has also been suggested that pregabalin's role in prevention of PONV is a product of postoperative opioid reduction.[13,14] However, a meta-analysis did not support this and probably the antiemetic mechanism of pregabalin is multifactorial in nature.[5]

The important risk factors for PONV are female gender, non-smoking status, history of PONV, motion sickness, age and postoperative opioids.[11] In our study, the treatment groups were comparable with respect to these factors.

The number of occurrence of nausea within 2-24 hours of surgery among patients in pregabalin group was lower whereas no episode of vomiting was reported in either groups during 2-hours to 24-hours period. A meta-analysis that included 23 studies involving 1693 participants, found that preoperative pregabalin was associated with a significantly reduced incidence of nausea, vomiting and rescue antiemetic administration.[5] A significant reduction in the incidence of postoperative nausea (NNT=10.1) and vomiting (NNT=11.3) following hysterectomy was also observed with pregabalin.[15]

A meta-analysis found that pregabalin can reduce the occurrence of nausea and vomiting after laparoscopic cholecystectomy.[16] Another review revealed that the administration of pregabalin was associated with a lower incidence of PONV at 24 hours when compared with control and the incidence reduced significantly by 38%, relative to placebo at 24 hours after surgery.[14] We have compared our results only with the studies conducted for different types of surgeries in which pregabalin premedication was administered. Most of these studies and meta analyses actually focused on the effect of pregabalin premedication as a preemptive analgesic. This way our study is quite different to the others referred to in our analysis.

The high incidence of PONV may justify the use of prophylactic antiemetics for its prevention after middle ear surgery. Various other antiemetics, such as 5-HT3 antagonists, dopamine receptor antagonists, and antihistamine drugs have been studied for the prevention of PONV after middle ear surgery. However, each of these treatments is associated with critical limiting factors and none of the available antiemetics is entirely effective after middle ear surgery in adult patients.[4]

Preoperative pregabalin is known to produce postoperative visual disturbances, sedation and somnolence.

An excessively sedated patient in the postoperative period is not desirable. Gabapentinoids are known to cause dizziness and visual disturbance that are more frequent with pregabalin than with gabapentin.[17] In our study, the sedative score was significantly higher in pregabalin as compared to ondansetron at each point of time. Also, we observed a significant decrease of sedation score over time and there was no sedative signs at 24-hours. However, none of the patients required any intervention.

A meta-analysis indicated that there was no significant difference in the occurrence of sedation with pregabalin.[15] Lam *et al* found that the incidence of adverse effects of pregabalin was not equal in different surgical categories.[18]

It also depends on the dose with no significant differences in the occurrences of respiratory depression, pruritus, dizziness, blurred vision, and headache found when the dose used was less than 300 mg.[16] A review revealed that the administration of pregabalin was associated with a significantly higher incidence of sedation (46% increase), dizziness (33% increase), and visual disturbance (3.5 times more likely) relative to placebo. Interestingly, pregabalin-treated patients achieved hospital discharge criteria 14 hours earlier than controls.[13]

Absorption of pregabalin after oral administration is quicker than gabapentin with a peak blood concentration reaching within an hour after ingestion.

That is why we decided to use the former in this study. We chose to study a single dose of 150 mg because the recommended starting dose is 150 mg/day.[19] A meta-analysis found that the time of administration of pregabalin was 1 or 2 hours before anaesthesia induction, and the dose of pregabalin ranged from 50 to 300 mg.[16] However, doses more than 300 mg are known to cause more side effects.[5]

We particularly watched for dizziness and somnolence, the most common side effects, because they generally begin shortly after initiation of dosing.

When PONV prophylaxis has failed within 6 hours, patients

should receive antiemetic treatment from a different pharmacological class.[1] However, if more than 6 hours has elapsed, administration of a second dose of 5-HT3 receptor antagonist may be considered.[1] There was a critical limitation of our study in terms of the relatively small size of our study that was conducted in a single centre. A placebo group was not included because denial of effective treatment is ethically not justified.[20] We did not incorporate a visual analog scale to quantify symptoms or a verbal rating scale for assessing patients' satisfaction. It has been suggested that only rigorous methods and reliable instruments yield valid and clinically relevant findings and not these simple scales.[21]

Future studies may focus on optimum dose required for a particular surgery for prevention of PONV. In conclusion, pregabalin 150 mg prophylaxis in patients undergoing mastoid surgery delays the onset and decreases the episodes of vomiting within 2-hours of surgery as compared to ondansetron 8 mg. It also reduces the incidence of nausea in the postoperative period, albeit with a higher incidence of sedation. Inclusion of pregabalin in multimodal therapy for prevention of PONV may lead to marked cost saving, keeping in view the reduced requirement of anaesthetics and analgesics among its other useful properties.

ACKNOWLEDGEMENTS

The authors express their gratitude to Dr. Alok Ranjan, PhD, Department of Community and Family Medicine, All India Institute of Medical Sciences, Patna, India for his help in statistical analysis.

Ethical Disclosures
Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship.
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

Responsabilidades Éticas
Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Received: 1th of January, 2022 | Submissão: 01 de janeiro, 2022
Accepted: 31st of May, 2022 | Aceitação: 31 de maio, 2022
Published: 29th of June, 2022 | Publicado: 29 de junho, 2022

REFERENCES

1. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2020;131:411-48. doi: 10.1213/ANE.0000000000004833.
2. Dubey P, Thapliyal GK, Ranjan A. A comparative study between ondansetron and gabapentin for prevention of postoperative nausea and vomiting following maxillofacial surgery. J Maxillofac Oral Surg. 2020;19:616-23. doi: 10.1007/s12663-020-01366-3.
3. Mukhopadhyay S, Niyogi M, Ray R, Mukhopadhyay BS, Dutta M, Mukherjee M. Betahistine as an add-on: The magic bullet for postoperative nausea, vomiting and dizziness after middle ear surgery?. J Anaesthesiol Clin Pharmacol. 2013;29:205-10. doi: 10.4103/0970-9185.111725.
4. Lee DW, Lee HG, Jeong CY, Jeong SW, Lee SH. Postoperative nausea and vomiting after mastoidectomy with tympanoplasty: a comparison between TIVA with propofol-remifentanil and balanced anesthesia with sevoflurane-remifentanil. Korean J Anesthesiol. 2011;61: 399-404. doi: 10.4097/kjae.2011.61.5.399.
5. Grant MC, Betz M, Hulse M, Zorrilla-Vaca A, Hobson D, Wick E, et al. The effect of preoperative pregabalin on postoperative nausea and vomiting: a meta-analysis. Anesth Analg. 2016;123:1100–7. doi: 10.1213/ANE.0000000000001404.
6. Apfel CC, Roewer N, Korttila K. How to study postoperative nausea and vomiting. Acta Anaesthesiol Scand. 2002;46:921-8. doi: 10.1034/j.1399-6576.2002.460801.x.
7. Kim KM, Huh J, Lee SK, Park EY, Lee JM. Combination of gabapentin and ramosetron for the prevention of postoperative nausea and vomiting after gynecologic laparoscopic surgery: a prospective randomized comparative study. BMC Anesthesiol. 2017;17:65. doi: 10.1186/s12871-017-0357-8.
8. Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, et al. Enhanced Recovery After Surgery Society. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clin Nutr. 2012;31:801-16. doi: 10.1016/j.clnu.2012.08.012.
9. Fink K, Dooley DJ, Meder WP, Suman-Chauhan N, Duffy S, Clusmann H, et al. Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology. 2002;42:229–36. doi: 10.1016/s0028-3908(01)00172-1.
10. Maneuf YP, Hughes J, McKnight AT. Gabapentin inhibits the substance P-facilitated K(+)-evoked release of [(3)H]glutamate from rat caudial trigeminal nucleus slices. Pain. 2001;93:191–6. doi: 10.1016/S0304-3959(01)00316-5.
11. Fehrenbacher JC, Taylor CP, Vasko MR. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. Pain. 2003;105:133–41. doi: 10.1016/s0304-3959(03)00173-8.
12. Dias JM, de Brito TV, de Aguiar Magalhães D, da Silva Santos PW, Batista JA, do Nascimento Dias EG, et al. Gabapentin, a synthetic analogue of gamma aminobutyric acid, reverses systemic acute inflammation and oxidative stress in mice. Inflammation. 2014;37:1826–36. doi: 10.1007/s10753-014-9913-2.
13. Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth. 2015;114:10–31. doi: 10.1093/bja/aeu293.
14. Eipe N, Penning J, Yazdi F, Mallick R, Turner L, Ahmadzai N, et al. Perioperative use of pregabalin for acute pain—a systematic review and meta-analysis. Pain. 2015; 156:1284–300. doi: 10.1097/j.pain.0000000000000173.
15. Wang Y, Xia M, Shan N, Yuan P, Wang DL, Shao JH, et al. Pregabalin can decrease acute pain and postoperative nausea and vomiting in hysterectomy. A meta-analysis. Medicine. 2017;96:e7714. doi: 10.1097/MD.0000000000007714.
16. Li S, Guo J, Li F, Yang Z, Wang S, Qin C. Pregabalin can decrease acute pain and morphine consumption in laparoscopic cholecystectomy patients: A meta-analysis of randomized controlled trials. Medicine. 2017;96:e6982. doi: 10.1097/MD.0000000000006982.
17. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, et al. Canadian Perioperative Anesthesia Clinical Trials (PACT) Group. Perioperative use of gabapentinoids for the management of postoperative acute pain: A systematic review and meta-analysis. Anesthesiology. 2020;133:265-79. doi: 10.1097/ALN.0000000000003428.
18. Lam DM, Choi SW, Wong SS, Irwin MG, Cheung CW. Efficacy of pregabalin in acute postoperative pain under different surgical categories: a meta-analysis. Medicine. 2015;94:e1944. doi: 10.1097/MD.0000000000001944.
19. Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA. A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. Anesth Analg. 2007;105:1449-53. doi: 10.1213/01.ane.0000286227.13306.d7.
20. Aspinall RL, Goodman NW. Denial of effective treatment and poor quality of clinical information in placebo controlled trials of ondansetron for postoperative nausea and vomiting: a review of published trials. BMJ. 1995;311:844–46. doi: 10.1136/bmj.311.7009.844.
21. Le May S, Hardy JF, Taillefer MC, Dupuis G. Patient satisfaction with anesthesia services. Can J Anaesth. 2001;48:153–61. doi: 10.1007/BF03019728.