Efficacy and safety of preemptive analgesia with gabapentinoids for patients undergoing arthroscopic shoulder surgery: a systematic review and meta-analysis

Eficacia y seguridad de la analgesia preventiva con gabapentinoides para pacientes sometidos a cirugía artroscópica de hombro: una revisión sistemática y metanálisis

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ABSTRACT. Objective: To assess the efficacy and safety of preemptive analgesia with gabapentinoids for patients undergoing arthroscopic shoulder surgery. **Material and methods:** A PRISMA-compliant systematic review and meta-analysis was conducted in PubMed, Cochrane Library and ScienceDirect databases. Randomized Controlled Trials (RCTs) comparing gabapentinoids (gabapentin and pregabalin) with placebo in patients undergoing shoulder arthroscopic surgery were retrieved. The primary endpoint was the visual analogue scale (VAS) score at 24 hours and cumulative morphine consumption at 24 hours. The secondary outcomes were complications of nausea/vomiting, sedation and dizziness. After tests for publication bias and heterogeneity among studies were performed, data were aggregated for random-effects models when necessary. **Results:** Five clinical studies (gabapentin group n = 4 and pregabalin group n = 1) were ultimately included in the meta-analysis. Gabapentinoids were associated with reduced pain scores at 24 hours. Similarly, gabapentinoids were associated with a reduction in cumulative morphine consumption at 24 hours. Furthermore, gabapentinoids can significantly reduce the occurrence of nausea/vomiting. There were no significant differences in the occurrence of sedation and dizziness. **Conclusions:** Preoperative use of

RESUMEN. Objetivo: Evaluar la eficacia y seguridad de la analgesia preventiva con gabapentinoides para pacientes sometidos a cirugía artroscópica del hombro. **Material y métodos:** Se llevó a cabo una revisión sistemática y metaanálisis conforme a PRISMA en las bases de datos PubMed, Cochrane Library y ScienceDirect. Se recuperaron ensayos controlados aleatorios (RCT) que comparaban los gabapentinoides (gabapentina y pregabalina) con placebo en pacientes sometidos a cirugía artroscópica del hombro. El punto final principal fue la puntuación de la escala analógica visual (VAS) a las 24 horas y el consumo acumulado de morfina a las 24 horas. Los resultados secundarios fueron complicaciones de náuseas/vómitos, sedación y mareos. Después de realizar pruebas de sesgo de publicación y heterogeneidad entre los estudios, se agregaron datos para modelos de efectos aleatorios cuando fue necesario. **Resultados:** En última instancia, se incluyeron en el metaanálisis cinco estudios clínicos (grupo de gabapentina n = 4 y grupo de pregabalina n = 1). Los gabapentinoides se asociaron con puntuaciones de dolor reducidas a las 24 horas. Del mismo modo, los gabapentinoides se asociaron con una reducción en el consumo acumulado de morfina a las 24 horas. Además, los gabapentinoides pueden reducir significativamente la aparición de náuseas/vómitos. No hubo diferencias significativas en la ocurrencia de sedación y ma-

Level of evidence: I

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gabapentinoids was able to reduce postoperative pain, total morphine consumption, and morphine-related complications following arthroscopic shoulder surgery. Further studies should determine the optimal dose and whether pregabalin is superior to gabapentin in controlling acute pain after shoulder surgery.

Keywords: Preemptive analgesia, gabapentin, pregabalin, shoulder arthroscopy.

reos. **Conclusiones:** El uso preoperatorio de gabapentinoides fue capaz de reducir el dolor postoperatorio, el consumo total de morfina y las complicaciones relacionadas con la morfina después de la cirugía artroscópica del hombro. Otros estudios deben determinar la dosis óptima y si la pregabalina es superior a la gabapentina en el control del dolor agudo después de la cirugía de hombro.

Palabras clave: Analgesia preventiva, gabapentina, pregabalina, artroscopia de hombro.

Introduction

Pain is an unpleasant sensation associated with sensory and emotional experiences that can cause potential or actual tissue damage.[1] Pain after surgery is a maladaptive response that can diminish a patients quality of life.[2,3] Acute postoperative pain is an important predictive factor for chronic post-surgical pain, which is observed in 10-65% of patients after surgery. Therefore, controlling pain after surgery is very important.[4]

The purpose of preemptive analgesia is to reduce postoperative pain, contributing to a more comfortable recovery period and reducing the need for narcotic pain control.[1] It refers to the administration of analgesic treatment before surgical incision or tissue injury. It is based on the concept that central and peripheral sensitizations are the major causes of hypersensitivity to pain after injury.[1,4,5,6]

Agents used in preemptive analgesia include NSAIDs, the neuromodulatory agents gabapentin and pregabalin, acetaminophen, and extended-action local anesthesia. Also, multimodal regimens were developed to reduce opioid consumption and associated adverse effects.[7]

Preemptive analgesia has been used in orthopedic surgery for total knee and hip arthroplasty, spine instrumentation and fusion, lumbar discectomy, hallux valgus, femoral neck fractures, and knee, shoulder and hip arthroscopy.[4]

Gabapentinoids drugs (gabapentin and pregabalin) were developed originally as anticonvulsants and subsequently found to be effective in neuropathic and postoperative pain management.[8,9,10,11,12] Pregabalin compared to gabapentin has a better pharmacokinetic profile with rapid absorption, higher bioavailability, and less intersubject variability.[8,13] Gabapentin has been used in preemptive analgesia for the treatment of thoracotomy, total knee replacement, total hip replacement, mastectomy, lumpectomy, video-assisted thoracoscopic surgery, hand surgery, carpal tunnel surgery, knee arthroscopy, shoulder arthroplasty and shoulder arthroscopy.[14] Pregabalin has been used in preemptive analgesia for the treatment of laparoscopic cholecystectomy, laparoscopic hysterectomy, arthroscopic Bankart repair, arthroscopic rotator cuff repair, lumbar fusion surgery, total knee arthroplasty, septoplasty, laparoscopic prostatectomy, radical neck dissection surgery, lower limb orthopedic surgery, molar extraction and endoscopic thyroidectomy.[9,15,16,17,18,19,20,21,22,23,24,25,26]

Shoulder arthroscopy is a frequent and safe procedure for numerous pathologies and is suited to day-surgery, the difficulty lies in managing pain and the side effects of anesthetic and analgesic drugs.[27]

The purpose of this review was to assess the efficacy and safety of preemptive analgesia with gabapentinoid drugs for patients undergoing arthroscopic shoulder surgery.

Material and methods

This systematic review was reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. As this is an analysis of previously published articles, participant informed consent and ethical approval are not required.

Search strategy

Two researchers search the relevant studies independently including PubMed (1966-017.12), ScienceDirect (1985-017.12), and the Cochrane Library for potentially relevant studies. Reference lists of all the potential included studies and relevant reviews were hand-searched for any additional trials. Only published articles that had been originally written in English or translated into English were considered. The Mesh terms and appropriate or corresponding terms used in the search and Boolean operators employed were as follows: «gabapentin» or «pregabalin» [Mesh], and «preemptive» and «analgesia» [Mesh] and «arthroscopy» [Mesh] and «shoulder» [Mesh].

Eligibility criteria and study selection

1. Participants, patients diagnosed with shoulder pathology undergoing arthroscopic surgery, regardless of age and gender.
2. Intervention, administration of gabapentinoids prior to surgical intervention.
3. Comparison, placebo administration.
4. Outcomes, weighted 10-point pain scores after 24 hours after surgery was the primary outcome. Secondary outcomes included opioid consumption 24 hours after surgery, as well as complication rates.
5. Study design, only RCTs were included.

All searches were limited to human subjects. Eligible studies were assessed independently by 2 authors. A 3rd reviewer acted as a judge if there was any disagreement.

Data extraction

A standard data extraction form was designed using Microsoft Excel, and data were independently extracted from the included studies by 2 reviewers (C-VA and L-VJ). The following data were extracted: author, publication year, sample size, age, gender, drug administered and dosage, and outcomes. The primary endpoints included the following: weighted 10-point pain scores after 24 hours, (0 indicated «no pain» and 10 indicated the «worst imaginable pain»); and incidence of nausea/vomiting, sedation and dizziness. Data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval (CI)) were converted to the mean ± standard deviation (SD) according to the Cochrane Handbook[28] if the data were not reported numerically, we extracted these data using the GetData Graph Digitizer software from the published figures. All data were extracted by 2 independent reviewers, and disagreements were resolved by discussion.

Quality assessment

The methodological quality of all included trials was independently assessed by 2 reviewers using the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://handbook.cochrane.org/). A total of 7 items (random sequence generation, allocation concealment, blinding to the participant and personnel, blinding to the outcome assessment, incomplete outcome, selective reporting, and other bias) were measured. Each of the items was measured as «low risk of bias», «unclear risk of bias», and «high risk of bias». The risk of bias summary and risk of bias graph were obtained using Review Manager (RevMan) [Computer program]. Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Statistical analyses

Continuous outcomes (weighted 10-point pain scores after 24 hours and opioid consumption at 24 hours) were expressed as the weighted mean differences (WMD) and respective 95% CI. Dichotomous outcomes (occurrence of nausea/vomiting, sedation and dizziness) were expressed as the risk ratio (RR) with 95% CI. Statistical significance was set at $p < 0.05$ to summarize the findings across the trials. The meta-analysis was calculated by RevMan, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Statistical heterogeneity was tested using the χ^2 test and I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $p > 0.1$), a fixed-effects model was adopted; otherwise, a random-effects model was chosen.
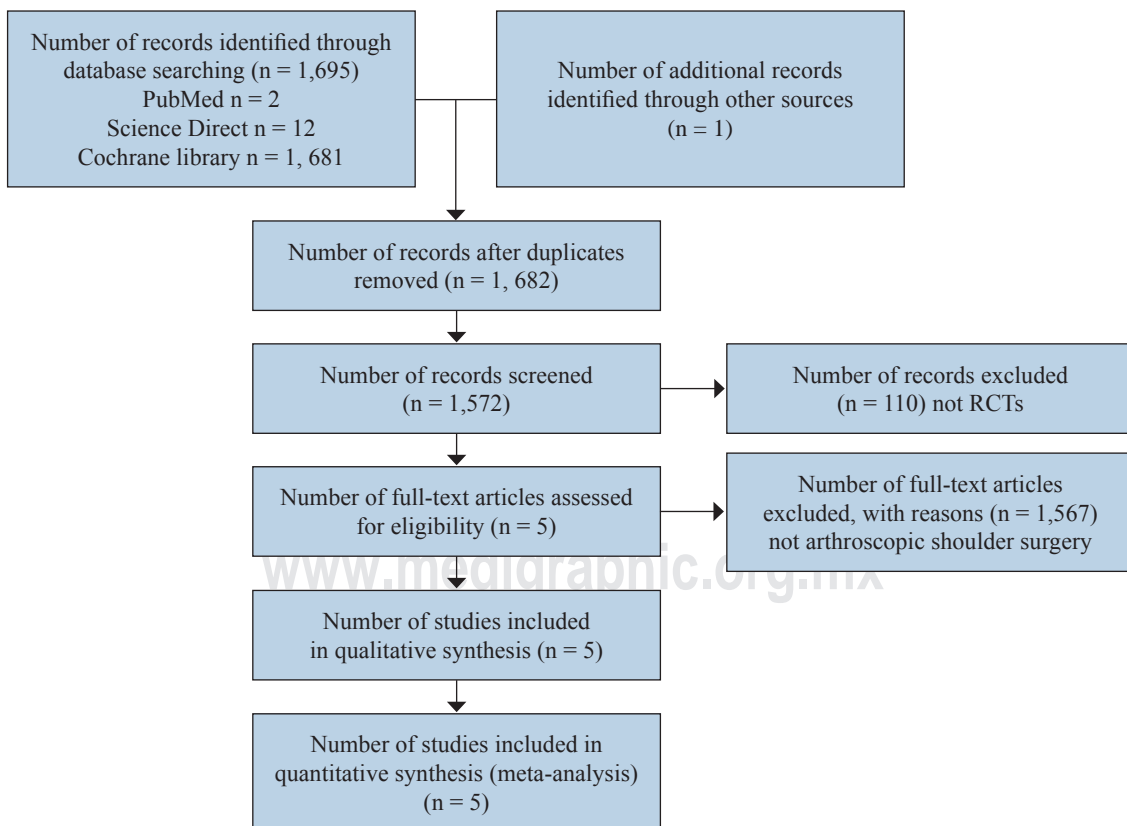

Figure 1: PRISMA flow diagram of the included studies.

Table 1: General characteristics of the included studies.

| | Age (years) | | Male (%) | | | Intervention | | | | | |
Reference	Experi-mental	Control	Experi-mental	Control	No. Patients	Dose and intervals	Total dose (mg)	Control	Outcomes*	Follow-up (hours)	Study**
Adam	43	47	66.6	69.2	53	Gabapentin 800 mg 2 hours before surgery	800	Placebo (n=26)	1,2,3,4	48	RCT
Ahn	55	51	43	43	60	Pregabalin 150 mg 1 hour before induction of anesthesia	150	Placebo (n=30)	1,2,3,4,5	48	RCT
Bang	56.3	59.5	34.7	39.1	46	Gabapentin 300 mg 2 hour before surgery	300	Placebo (n=23)	1,2,3,4,5	24	RCT
Mardani-Kivi	30.2	28.3	72.9	88.2	71	Gabapentin 600 mg 2 hour before surgery	600	Placebo (n=34)	1,3,4,5	24	RCT
Spence	31.8	31.5	84.6	83.9	57	Gabapentin 300 mg 1 hour before surgery, then 300 mg the first night postoperative and 300 mg BID for 48 hours	1,800	Placebo (n=31)	1,2	48	RCT

* 1 = VAS at 24 hours, 2 = Total morphine consumption, 3 = Nausea/vomiting, 4 = Sedation, 5 = Dizziness.
** RCT = Randomized controlled trial.

Results

Search results

In the initial research, a total of 1695 papers were identified from the electronic databases (PubMed = 2, ScienceDirect = 12, Cochrane Library = 1681); 1 additional record was identified through other sources. Thus, a total of 1696 papers were obtained in the initial search. These bibliographical references were introduced into Mendeley Software (Version 1.19, Elsevier, CA). Duplicates were then removed and 1682 papers were reviewed. After screening the titles and abstracts of these 1682 studies, 1677 papers were excluded because they were irrelevant or did not meet the criteria. Ultimately, 5 clinical studies were included in the meta-analysis. The flow diagram for the included studies is provided in *Figure 1*.

Study characteristics and bias assessment

The general information of the patients is shown in *Table 1*. The publication years ranged from 2006 to 2016. The numbers of gabapentinoids and control subjects ranged from 46 to 71. The total gabapentinoids dosages ranged from 150 to 1,200 mg per day. Finally, the follow-up times ranged from 24 to 48 hours. The general characteristics of the included studies were comparable and all studies describe the intent to treat analyses.

The risk of bias summary and risk of bias graph are provided in *Figures 2 and 3*, respectively. The risk of bias for selective reporting was unclear in 1 study[29] and low in 4 studies.[17,30,31,32] The rest all had low risk of bias.[17,29,30,31,32]

Results of meta-analysis

VAS at 24 hours postoperative

Postoperative VAS scores at 24 hours were reported in 5 studies, and the pooled results indicated that preemptive administration of gabapentinoids was associated with reduced VAS at 24 hours; this corresponded to a reduction of 0.77 points (WMD = -0.77, 95% CI -1.49, -0.05, p = 0.04 *(Figure 4)*) at 24 hours on a 10-point visual analogue score.

Total morphine-equivalent consumption at 24 hours

Morphine-equivalent consumption at 24 hours was reported in 4 studies, and the pooled results indicated that preoperative administration of gabapentinoids
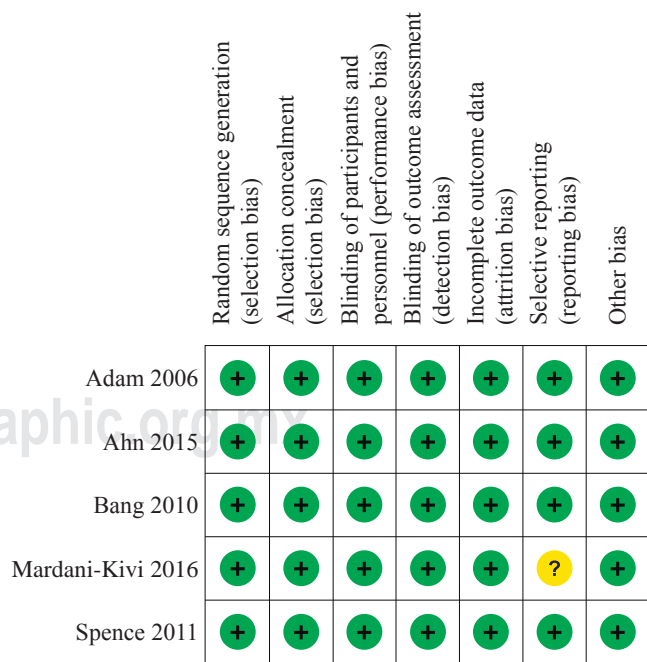

Figure 2: Risk of bias summary of the included trials. +, low risk; -, high risk; ?, risk unclear.
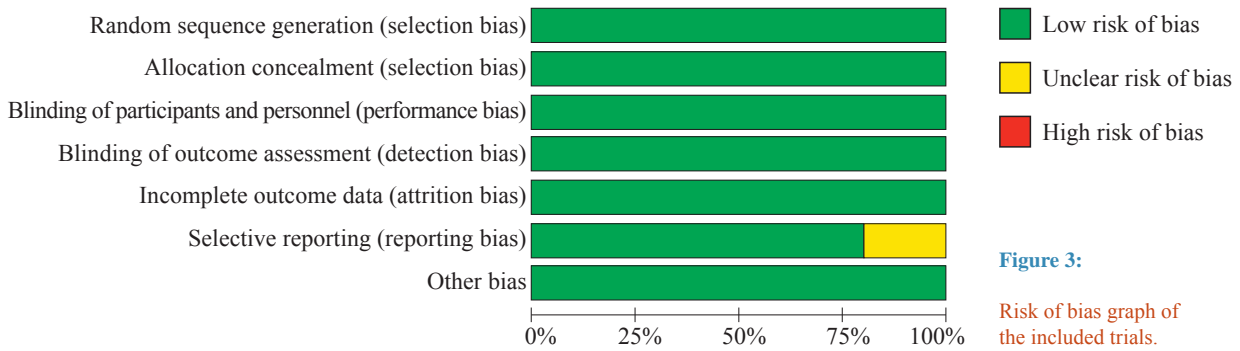
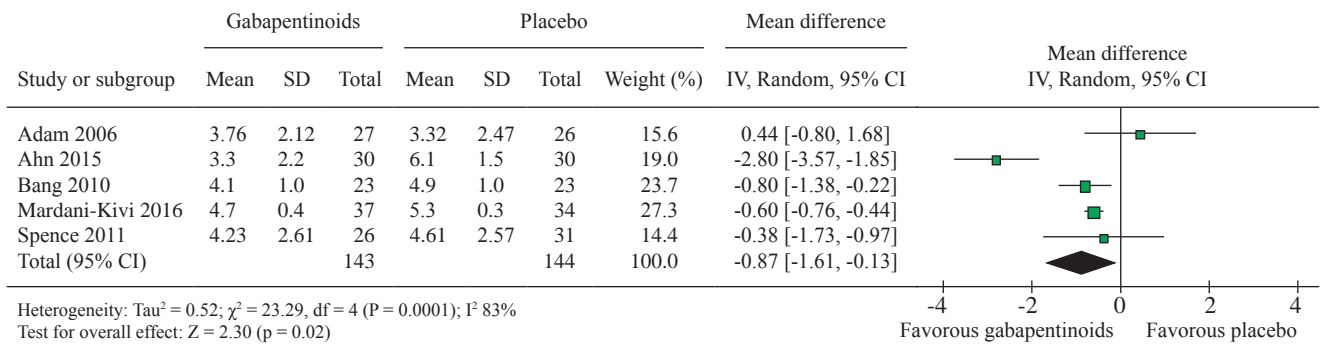**Figure 3:** Risk of bias graph of the included trials.

Figure 4: Forest plot comparing visual analogue scale at 24 hours between the gabapentinoids group and the control group.
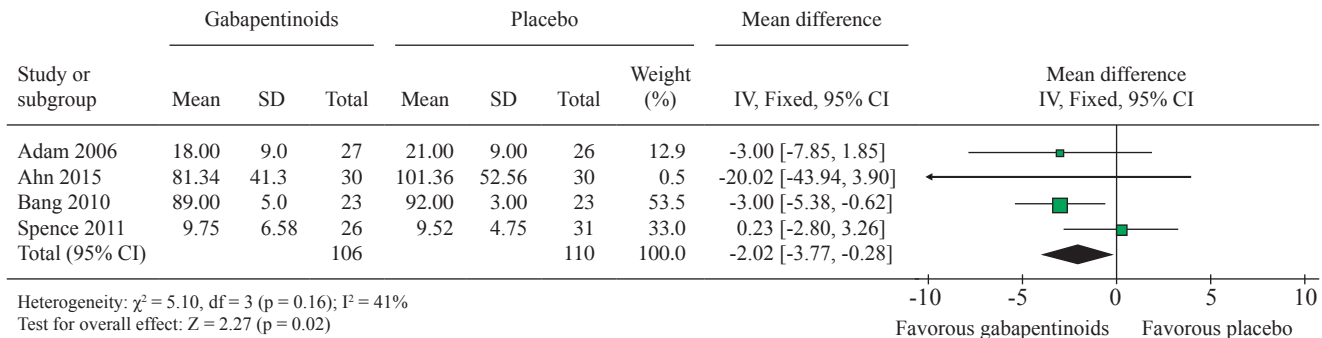

Figure 5: Forest plot comparing cumulative morphine-equivalent consumption at 24 hours between the gabapentinoids group and he control group.

was associated with reduced morphine-equivalent consumption at 24 hours; this corresponded to a reduction of 2.02 mg (WMD = -2.02, 95% CI -3.77, -0.28, p = 0.02 *(Figure 5)*) at 24 hours of oral morphine equivalent daily dose.

Complications

There was no significant difference in the occurrence of dizziness (RR = 1.27, 95% CI 0.75, 2.16, p = 0.37, *(Figure 6)*) or sedation (RR = 1.19, 95% CI 0.62, 2.27, p = 0.61 *(Figure 7)*). Gabapentinoids can significantly reduce the occurrence of nausea/vomiting (RR = 0.60, 95% CI 0.36, 1.00, p = 0.05 *(Figure 8)*).

Subgroup analysis

Given the fact that only one study focused on pregabalin and that the other four studies didn't use the same dose of gabapentin, a subgroup analysis could not be performed.

Discussion

The current meta-analysis demonstrated that the use of gabapentinoids is associated with reduced pain scores at 24 hours postoperatively, which is equivalent on a 10-point VAS to 0.77 points, which, even though is statistically significant, may not be clinically relevant. The cumulative morphine-equivalent consumption at 24 hours was reduced

in the gabapentinoids group by approximately 2.02 mg. The most important finding of this meta-analysis was that gabapentinoids can reduce the occurrence of nausea/vomiting after arthroscopic shoulder surgery. There was no significant difference in terms of sedation and dizziness.

A major strength of the current meta-analysis was that we comprehensively searched the electronic databases (PubMed, Cochrane Library, and ScienceDirect databases) and calculated the relevant outcomes in a statistically rigorous method. We included RCTs and excluded non-RCTs, and thus the selective risk of bias was largely eliminated. The quality of the included RCTs was high or moderate.

Pooled results indicated that preoperative administration of gabapentinoids was associated with a significant reduction of acute pain at 24 hours following arthroscopic

shoulder surgery. These results were in contrast to the Hamilton et al study,[33] in which the authors found no evidence to support the routine use of gabapentinoids in the management of acute pain following total knee arthroplasty (TKA) after evaluating 12 RCTs. Mao et al[34] performed a meta-analysis of 7 RCTs and found that gabapentinoids were associated with lower pain scores, morphine consumption, and postoperative nausea and vomiting (PONV) following total hip arthroplasty. Liu et al[35] performed a meta-analysis of 16 RCTs and found that gabapentinoids were associated with reduced pain scores at 6, 12, 24, and 48 hours. Similarly, gabapentinoids were associated with a reduction in cumulative morphine consumption at 24 and 48 hours. Furthermore, gabapentinoids can significantly reduce the occurrence of nausea, vomiting, and pruritus. There were no significant differences in the occurrence of sedation,
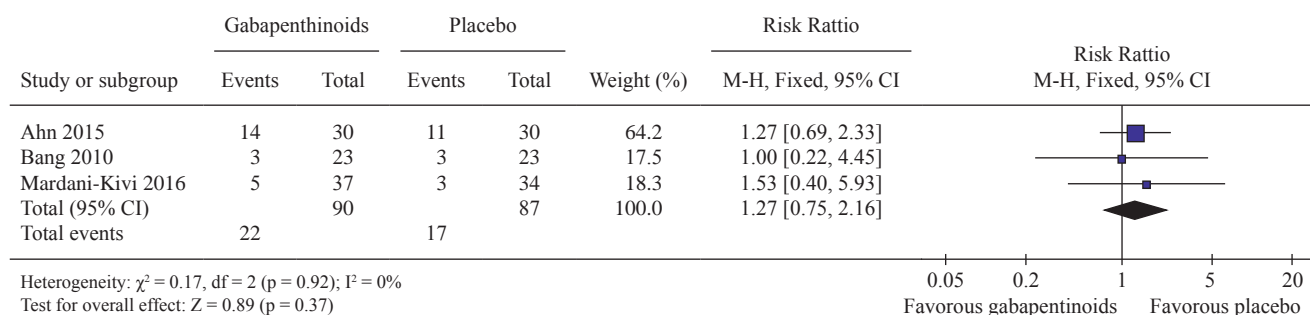
Study or subgroup	Gabapenthinoids		Placebo		Weight (%)	Risk Rattio M-H, Fixed, 95% CI	Risk Rattio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Ahn 2015	14	30	11	30	64.2	1.27 [0.69, 2.33]	
Bang 2010	3	23	3	23	17.5	1.00 [0.22, 4.45]	
Mardani-Kivi 2016	5	37	3	34	18.3	1.53 [0.40, 5.93]	
Total (95% CI)		90		87	100.0	1.27 [0.75, 2.16]	
Total events	22		17				

Heterogeneity: $\chi^2 = 0.17$, df = 2 (p = 0.92); $I^2 = 0\%$
Test for overall effect: Z = 0.89 (p = 0.37)

Figure 6: Forest plot comparing dizziness between the gabapentinoids group and the control group.

Study or subgroup	Gabapenthinoids		Placebo		Weight (%)	Risk Rattio M-H, Fixed, 95% CI	Risk Rattio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Adam 2006	9	27	8	26	61.6	1.08 [0.49, 2.38]	
Ahn 2015	3	30	2	30	15.1	1.50 [0.27, 8.34]	
Bang 2010	1	23	1	23	7.6	1.00 [0.07, 15.04]	
Mardani-Kivi 2016	3	37	2	34	15.7	1.38 [0.24, 7.76]	
Total (95% CI)		117		113	100.0	1.19 [0.62, 2.27]	
Total events	16		13				

Heterogeneity: $\chi^2 = 0.17$, df = 3 (p = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 0.52 (p = 0.61)
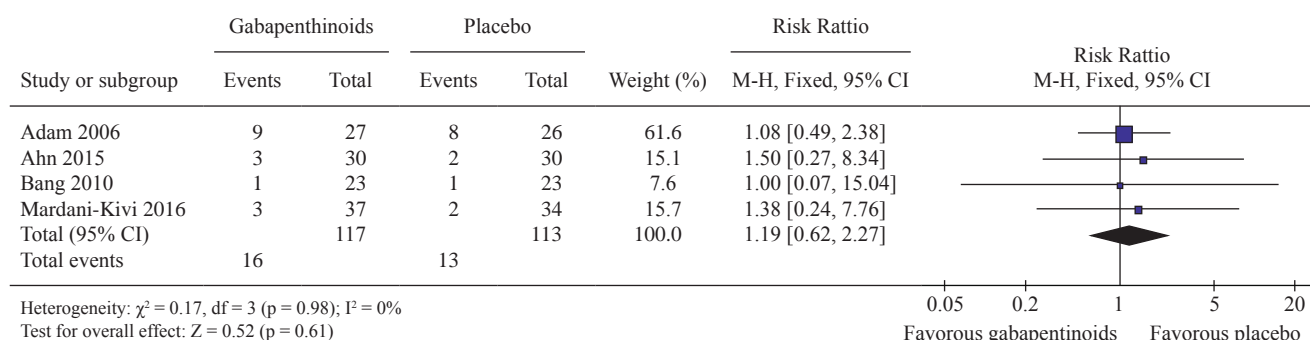
Figure 7: Forest plot comparing sedation between the gabapentinoids group and the control group.

Study or subgroup	Gabapenthinoids		Placebo		Weight (%)	Risk Rattio M-H, Fixed, 95% CI	
	Events	Total	Events	Total			
Adam 2006	2	27	4	26	14.5	0.48 [0.10, 2.41]	
Ahn 2015	7	30	11	30	39.1	0.64 [0.29, 1.42]	
Bang 2010	7	23	11	23	39.1	0.64 [0.30, 1.35]	
Mardani-Kivi 2016	1	37	2	34	7.4	0.46 [0.04, 4.84]	
Total (95% CI)		117		113	100.0	0.60 [0.36, 1.00]	
Total events	17		28				

Heterogeneity: $\chi^2 = 0.16$, df = 3 (p = 0.98); $I^2 = 0\%$
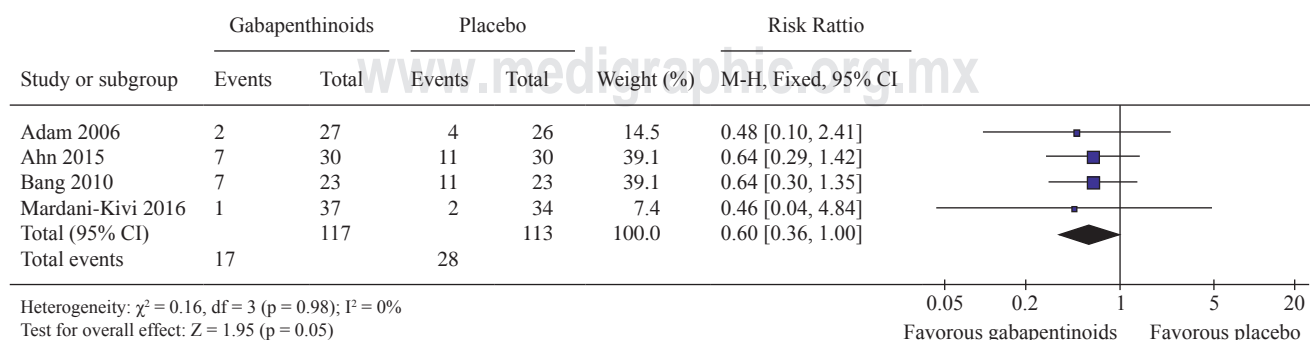Test for overall effect: Z = 1.95 (p = 0.05)

Figure 8: Forest plot comparing nausea/vomiting between the gabapentinoids group and the control group.

dizziness, headache, visual disturbances, somnolence, or urine retention. Jiang et al[36] reported that preoperative use of pregabalin was efficacious in the reduction of postoperative pain, total morphine consumption, and the occurrence of nausea following spine surgery. However, the sample size and the number of included studies were limited. Dong et al[37] performed a meta-analysis of RCTs on the use of pregabalin for reducing pain after TKA and found that pregabalin was effective in reducing pain intensity, the occurrence of nausea and vomiting but increase the occurrence of dizziness and sedation after TKA. Li et al[37] conducted a meta-analysis of 7 RCTs on the use of pregabalin as preemptive analgesia for TKA and THA and found that pregabalin was found to improve pain control at 24 and 48 hours with rest, reduce morphine consumption, improve the knee flexion degree, decrease the incident rate of nausea, vomiting, and pruritus, and increase the incident rate of dizziness after TKA and THA but could not improve the pain control at 72 hours with rest. Yu et al[38] conducted a meta-analysis of 7 RCTs on the use of gabapentin and pregabalin as preemptive analgesia for lumbar spine surgery and found that gabapentin and pregabalin can reduce pain intensity at 6, 12 and 24 hours after surgery.

There were several limitations to this meta-analysis: other perioperative pain management protocols were used in all of the studies; shoulder function outcomes were not reported in the included studies and whether better pain control was correlated with preferable shoulder outcomes was unknown; the dosage and interval of gabapentinoid administration differed between the studies, the optimal dose of gabapentinoids required further study; we only identified the published papers about the gabapentinoids versus control groups, so unpublished papers may influence the final results; and none of the studies directly compared gabapentin with pregabalin in arthroscopic shoulder surgery.

Conclusion

This is the first meta-analysis to compare the preoperative use of gabapentinoids versus a placebo for the management of pain after arthroscopic shoulder surgery. Analgesic efficacy and opioid-sparing effects were observed with the administration of gabapentinoids. Additionally, a significant decrease in the risk of nausea and vomiting was associated with the use of gabapentinoids. The optimal dose and dosing intervals of gabapentinoids will require further study.

References

1. Penprase B, Brunetto E, Dahmani E, Forthoffer JJ, Kapoor S. The efficacy of preemptive analgesia for postoperative pain control: a systematic review of the literature. *AORN J*. 2015; 101: 94-105.e8. doi: 10.1016/j.aorn.2014.01.030.
2. Bernal-Fortich LD, Aguilar CA, Rivera-Villa AH, Galindo-Avalos J, Aguilera-Martínez P, Torres-González R, et al. A prospective randomized trial of total synovectomy versus limited synovectomy in primary total knee arthroplasty: evaluation of bleeding, postoperative pain, and quality of life with SF-12 v2. *Eur J Orthop Surg Traumatol*. 2018; 28(4): 701-6. doi: 10.1007/s00590-018-2139-5

3. Galindo-Avalos J, Medina-Pontaza O, López-Valencia J, Gómez-Gómez JM, Colin-Vázquez A, Torres-González R. Functional outcomes and health-related quality of life after open repair of rotator cuff tears: a prospective cohort study. *Clin Trials Orthop Disord*. 2018; 3: 1-6. doi: 10.4103/2542-4157.227045.
4. Lopez VJ, Koch LA Preemptive analgesia in orthopedic surgery: a literature review. *Clin Trials Orthop Disord*. 2017; 2: 144 . doi: 10.4103/2542-4157.219377.
5. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia. *Plast Reconstr Surg*. 2014; 134: 85S-3. doi: 10.1097/PRS.0000000000000671.
6. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. *Can J Anesth Can d'anesthésie*. 2001; 48(11): 1091-101. doi: 10.1007/BF03016591.
7. Kurd MF, Kreitz T, Schroeder G, Vaccaro AR. The role of multimodal analgesia in spine surgery. *J Am Acad Orthop Surg*. 2017; 25: 260-8. doi: 10.5435/JAAOS-D-16-00049.
8. Kochhar A, Chouhan K, Panjiar P, Vajifdar H. Gabapentinoids as a part of multi-modal drug regime for pain relief following laproscopic cholecystectomy: a randomized study. *Anesth Essays Res*. 2017; 11: 676-80. doi: 10.4103/0259-1162.204208.
9. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. *Br J Anaesth*. 2011; 106: 454-62.
10. Kong VK, Irwin MG. Gabapentin: a multimodal perioperative drug? *Br J Anaesth*. 2007; 99: 775-86. doi: 10.1093/bja/aem316.
11. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg*. 2007; 104(6): 1545-56. doi: 10.1213/01.ane.0000261517.27532.80
12. Ho K-Y, Gan TJ, Habib AS. Gabapentin and postoperative pain – a systematic review of randomized controlled trials. *Pain*. 2006; 126: 91-101. doi: 10.1016/j.pain.2006.06.018.
13. Gajraj NM. Pregabalin: its pharmacology and use in pain management. *Anesth Analg*. 2007; 105: 1805-15. doi: 10.1213/01.ane.0000287643.13410.5e.
14. Hah J, Mackey SC, Schmidt P, McCue R, Humphreys K, Trafton J, et al. Effect of perioperative gabapentin on postoperative pain resolution and opioid cessation in a mixed surgical cohort: a randomized clinical trial. *JAMA Surg*. 2018;. 153(4): 303-11.
15. Trabulsi EJ, Patel J, Viscusi ER, Gomella LG, Lallas CD. Preemptive multimodal pain regimen reduces opioid analgesia for patients undergoing robotic-assisted laparoscopic radical prostatectomy. Urology. 2010; 76(5): 1122-4. doi: 10.1016/j.urology.2010.03.052.
16. Karaca O, Pinar HU, Turk E, Dogan R, Ahiskalioglu A, Solak SK. Effects of single-dose preemptive pregabalin and intravenous ibuprofen on postoperative opioid consumption and acute pain after laparoscopic cholecystectomy. *J Invest Surg*. 2019; 32(3): 189-95. doi: 10.1080/08941939.2017.1386738.
17. Ahn S, Byun SH, Park K, Ha JL, Kwon B, Kim JC. Analgesic efficacy of preemptive pregabalin administration in arthroscopic shoulder surgery: a randomized controlled trial. *Can J Anaesth*. 2016; 63(3): 283-9. doi: 10.1007/s12630-015-0510-0.
18. Domínguez DJ, Torres FD, Elizalde ME, Morales de los Santos R, Pérez CJ, Moheno GA, et al. Pyogenic cervical spondylodiskitis: case report and current literature review. *MOJ Orthop Rheumatol*. 2018; 10: 39-43. doi: 10.15406/mojor.2018.10.00383.
19. Amiri HR, Mirzaei M, Beig Mohammadi MT, Tavakoli F. Multi-modal preemptive analgesia with pregabalin, acetaminophen, naproxen, and dextromethorphan in radical neck dissection surgery: a randomized clinical trial. *Anesth Pain Med*. 2016; 6(4): e33526. doi: 10.5812/aapm.33526.
20. Lee JK, Chung KS, Choi CH. The effect of a single dose of preemptive pregabalin administered with COX-2 inhibitor: a trial in total knee arthroplasty. *J Arthroplasty*. 2015; 30(1): 38-42. doi: 10.1016/j.arth.2014.04.004.
21. Kim JH, Seo MY, Hong SD, Lee J, Chung SK, Kim HY, et al. The efficacy of preemptive analgesia with pregabalin in septoplasty. *Clin Exp Otorhinolaryngol*. 2014; 7(2): 102-5. doi: 10.3342/ceo.2014.7.2.102.
22. Bafna U, Rajarajeshwaran K, Khandelwal M, Verma AP. A comparison of effect of preemptive use of oral gabapentin and pregabalin for acute post-operative pain after surgery under spinal anesthesia. *J*

Anaesthesiol Clin Pharmacol. 2014; 30(3): 373-7. doi: 10.4103/0970-9185.137270.

23. Bindu M, Kumar AA, Kesavan M, Suresh V. Effect of preoperative pregabalin on postoperative pain relief in thyroidectomy patients: a prospective observational study. *Anesth Essays Res*. 2015; 9(2): 161-6. doi: 10.4103/0259-1162.156292.

24. Kim SI, Ha KY, Oh IS. Preemptive multimodal analgesia for postoperative pain management after lumbar fusion surgery: a randomized controlled trial. *Eur Spine J*. 2016; 25(5): 1614-9. doi: 10.1007/s00586-015-4216-3.

25. Sebastian B, Talikoti AT, Nelamangala K, Krishnamurthy D. Effect of oral pregabalin as preemptive analgesic in patients undergoing lower limb orthopedic surgeries under spinal anaesthesia. *J Clin Diagn Res*. 2016; 10(7): UC01-4. doi: 10.7860/JCDR/2016/18854.8081.

26. Asgari Z, Rouholamin S, Nataj M, Sepidarkish M, Hosseini R, Razavi M. Dose ranging effects of pregabalin on pain in patients undergoing laparoscopic hysterectomy: a randomized, double blinded, placebo controlled, clinical trial. *J Clin Anesth*. 2017; 38: 13-7. doi: 10.1016/j.jclinane.2017.01.015.

27. Boissard M, Crenn V, Noailles T, Campard S, Lespagnol F. Recovery after shoulder arthroscopy: Inpatient versus outpatient management. *Orthop Traumatol Surg Res*. 2018; 104(1): 39-43. doi: 10.1016/j.otsr.2017.10.010.

28. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011], 2011.

29. Mardani-Kivi M, Karimi Mobarakeh M, Keyhani S, Haghighi M, Hashemi-Motlagh K, Saheb-Ekhtiari K. Arthroscopic bankart surgery: does gabapentin reduce postoperative pain and opioid consumption? A triple-blinded randomized clinical trial. *Orthop Traumatol Surg Res*. 2016; 102: 549-53. doi: 10.1016/j.otsr.2016.01.028.

30. Adam F, Menigaux C, Sessler DI, Chauvin M. A single preoperative dose of gabapentin (800 milligrams) does not augment postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery. *Anesth Analg*. 2006; 103(5): 1278-82. doi: 10.1213/01.ane.0000237300.78508.f1.

31. Bang SR, Yu SK, Kim TH. Can gabapentin help reduce postoperative pain in arthroscopic rotator cuff repair? A prospective, randomized, double-blind study. *Arthroscopy*. 2010; 26(9 Suppl): S106-11. doi: 10.1016/j.arthro.2009.11.010.

32. Spence D, Goff J, Mohan E, Bowen K, Osborne L, Maye J. Perioperative administration of gabapentin for shoulder arthroscopy: a prospective, randomized, double-blind, placebo-controlled study. *AANA J*. 2011; 79(4 Suppl): S43-50.

33. Hamilton TW, Strickland LH, Pandit HG. A meta-analysis on the use of gabapentinoids for the treatment of acute postoperative pain following total knee arthroplasty. *J Bone Joint Surg Am*. 2016; 98(16): 1340-50. doi: 10.2106/JBJS.15.01202.

34. Mao Y, Wu L, Ding W. The efficacy of preoperative administration of gabapentin/pregabalin in improving pain after total hip arthroplasty: a meta-analysis. *BMC Musculoskelet Disord*. 2016; 17(1): 373. doi: 10.1186/s12891-016-1231-4.

35. Liu B, Liu R, Wang L. A meta-analysis of the preoperative use of gabapentinoids for the treatment of acute postoperative pain following spinal surgery. *Medicine (Baltimore)*. 2017; 96(37): e8031. doi: 10.1097/MD.0000000000008031.

36. Jiang H-L, Huang S, Song J, et al. Preoperative use of pregabalin for acute pain in spine surgery: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2017; 96(11): e6129. doi: 10.1097/MD.0000000000006129.

37. Dong J, Li W, Wang Y. The effect of pregabalin on acute postoperative pain in patients undergoing total knee arthroplasty: a meta-analysis. *Int J Surg*. 2016; 34: 148-60. doi: 10.1016/j.ijsu.2016.08.521.

38. Yu L, Ran B, Li M, Shi Z. Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. *Spine (Phila Pa 1976)*. 2013; 38(22): 1947-52. doi: 10.1097/BRS.0b013e3182a69b90.