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Review

Pre-medication with Gabapentin is associated with significant reductions in nausea and vomiting after shoulder arthroscopy: A meta-analysis

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ABSTRACT

Introduction: Arthroscopic shoulder surgery is increasingly performed as a day case procedure. Nausea, vomiting and inadequate pain control are the most frequent reasons for reattendance or failed discharge. Gabapentin is advocated as an adjunct to mitigate these symptoms and its use in shoulder arthroscopy may provide improved post-operative symptom control. The aim of this study was to perform a meta-analysis of studies evaluating the role of gabapentin in the peri-operative management of shoulder arthroscopy.
Hypothesis: Gabapentin is associated with significant improvements in post-operative nausea, vomiting and pain control after shoulder arthroscopy.
Material and methods: A systematic review using Medline was conducted in accordance with the PRISMA guidelines. Randomised controlled trials studies reporting on patients >15 years old receiving either preoperative gabapentin or placebo before any shoulder arthroscopic surgery were considered for eligibility. Studies were appraised against the Consolidated Standards of Reporting Trials (CONSORT) checklist. A meta-analysis was performed using Review Manager 5.3.
Results: Four randomized controlled trials were identified for inclusion ($n = 227$). Meta-analysis demonstrated a beneficial effect of gabapentin in preventing nausea and vomiting in the postoperative period (Odds Ratio 0.30, $p = 0.04$). However, pooled data analysis did not show significant advantage in using gabapentin for postoperative pain control ($p = 0.11$), although one study demonstrated a significant reduction in opioid consumption after gabapentin. No significant difference was reported in post-operative dizziness or sedation between the groups.
Discussion: Gabapentin did not show any significant benefit in postoperative pain control but is associated with significant reductions in post-operative nausea and vomiting after shoulder arthroscopy.
Level of evidence: I, meta-analysis.

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1. Introduction

Arthroscopic shoulder surgery is increasingly performed as a day case procedure [1]. Recent studies have evaluated complications and readmissions after ambulatory shoulder arthroscopy [2–4]. The knowledge gained has allowed more accurate prediction of total care costs whilst also highlighting opportunities to reduce morbidity [5]. Liu et al. [4] reported a 1.8% rate of hospital reviews within seven days of shoulder arthroscopy in a cohort of 103,476 patients. Frequent reasons for review included inadequate analgesia (23.8%), and nausea and vomiting. Christian et al. [2] also reported that pain and nausea were causes for failed discharge in 9% and 6% of cases respectively, whilst 7% of patients were readmitted within 30 days due to pain. Although the overall incidence of these adverse events is low, their occurrence can result in significant morbidity, considerable additional healthcare cost, and distress for the patient [4,6].

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Table 1
Search strategy for Medline.

Search Term	Number of studies
Gabapentin	4925
Gabapentinoids	192
#1 or #2	5027
Shoulder surgery	24,142
Shoulder arthroscopy	5082
#4 or #5	24,494
#3 AND #6	18
#7–only RCT	5

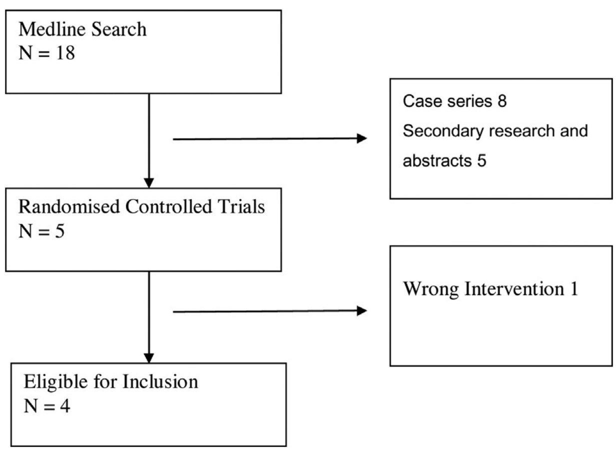

Fig. 1. Flow diagram of Medline review process.

Gabapentin has been advocated for use in post-operative pain management because it has antihyperalgesic and anxiolytic properties [7,8]. A recent meta-analysis has reported improvement in post-operative pain, nausea and vomiting after a wide variety of surgical procedures [6]. Despite the findings of this meta-analysis, numerous authors have not demonstrated an advantage of gabapentin in reducing pain or opioid requirements. Furthermore Grant et al. [6] only included a single study evaluating adverse events after shoulder arthroscopy. The aim of this study was therefore to perform a meta-analysis of studies evaluating the role of gabapentin in the peri-operative management of shoulder arthroscopy. The hypothesis of the study was that the use of gabapentin would be associated with significant reductions in peri-operative pain, nausea and vomiting.

2. Methods

A systematic review of the literature was conducted in accordance with the PRISMA guidelines using the online database Medline. The PRISMA checklist is illustrated in Appendix A. The review was registered on the PROSPERO database on 17 September 2018 (Reference number CRD42018104693). The searches were performed independently by two authors on the 12 September 2018 and repeated on the 30th of September 2018 in order to ensure accuracy. Any discrepancies were resolved through discussion between these two authors, with the senior author resolving any residual differences. The Medline search strategy used is illustrated in Table 1 and a flow diagram of the review process in Fig. 1.

Included studies were randomised controlled clinical trials published in the English language. The study must have evaluated the efficacy of pre-operative gabapentin for pain relief in patients undergoing shoulder arthroscopy. Any shoulder procedure performed through arthroscopic portals was included regardless of complexity. Any pre-operative regimen of gabapentin administration was acceptable providing dosing was clearly defined in study methodology and the study included a control group that had been randomized to receive pre-operative placebo treatment. To be eligible the study must have reported one of the two primary outcome measures, defined as either pain scores in the early post-operative period or reduction in post-operative opioid consumption. The early post-operative period was defined as the first 48 hours after the surgical procedure. Secondary outcome measures included the incidence of nausea and vomiting within 24 hours of surgery and post-operative side effects, including dizziness and drowsiness. Only primary research was considered for review with any abstracts, comments, review articles and technique articles excluded. The clinical studies were appraised independently by two authors with respect to the Consolidated Standards of Reporting Trials (CONSORT) checklist as illustrated in Table 2 [13]. Potential bias of studies was evaluated using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials [14] and are presented in Table 3.

A meta-analysis of the included trials was performed. Data for pain assessment and post-operative nausea and vomiting was pooled at either 24 or 48 hours after the surgical procedure dependent on the last reported time point in each study. The consumption of post-operative opioids could not be pooled given the heterogeneity in reporting different types of medications. Side effects of drowsiness and dizziness were pooled without a time point and were reported as being either present or not. For continuous data, the standardized mean difference was used to describe the size of the treatment effect, and, for dichotomous data, odds ratios were used. A random effects model was used for all analyses. The level of significance was set at $p < 0.05$. All statistical analyses were performed with Review Manager 5.3. Heterogeneity was measured and expressed as I^2.

3. Results

The search strategy is illustrated as a flow diagram in Fig. 1. After application of inclusion criteria, four randomised controlled trials were identified for inclusion ($n = 227$). Concise details of the included studies are given in Table 4.

4. Pain scores

Of the included studies, only Bang et al. [11] reported a significant reduction in pain intensity in the early post-operative period in the gabapentin group when compared to the placebo group. In this study patients underwent arthroscopic rotator cuff repair and both groups were provided with fentanyl via patient controlled analgesia (PCA) in addition to either gabapentin or placebo post-operatively. The VAS scores were significantly lower in the gabapentin group up until 12 hours ($p < 0.05$); at 2 hours (mean VAS 5 gabapentin group vs 7 placebo group), at 6 hours (4.4 vs 6) and 12 hours (4.3 vs 6.4). In contrast, Mardani et al. [9] reported on patients undergoing arthroscopic shoulder stabilization under general anaesthesia who were given pethidine for post-operative analgesia. The pain intensity was comparable between the two groups at 6 hours, mean VAS 4.9 (95% CI: 4.6–5.3) in the gabapentin group and 5.4 (95% CI: 5.0–5.7) in the placebo group, and at 24 hours they were 4.7(95% CI: 4.3–5.2) and 5.3 (95% CI: 4.9–5.6) respectively ($p > 0.05$). Similarly, Spence et al. [12] reported on patients undergoing a variety of arthroscopic shoulder procedures who all underwent general anaesthesia with an USS guided interscalene block. Post-operatively patients could receive up to 500 µg of IV fentanyl for pain and were discharged home with a combination of 5 mg of oxycodone and 325 mg of acetaminophen for analgesia. The average pain scores on post-operative day 1 (gabapentin group, 4.23 [SD:2.61] vs control group, 4.61 [SD:2.57]; $p = 0.58$)

Table 2
CONSORT 2010 checklist of information to include when reporting a randomised trial.

Section/Topic	Item No	Checklist item	Mardani [9]	Adams [10]	Bang [11]	Spence [12]
Title and abstract						
	1a	Identification as a randomised trial in the title	1	No	1	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1	1	1	No
Introduction						
Background and objectives	2a	Scientific background and explanation of rationale	1-2	1-2	1-2	2
	2b	Specific objectives or hypotheses	2	2	2	2
Methods						
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2	2	2	2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	2	N/A	N/A	N/A
Participants	4a	Eligibility criteria for participants	2	2	2	2
	4b	Settings and locations where the data were collected	2	2	2	2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	2	2	2	2-3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	2	2-3	2	3
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A	N/A	N/A	N/A
Sample size	7a	How sample size was determined	2	2	2	3
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A	N/A	N/A	N/A
Randomisation						
Sequence generation	8a	Method used to generate the random allocation sequence	2	2	2	2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	2	2	2	2
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	No	2	2	2
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2	2	2	2
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	2	2	2	2
	11b	If relevant, description of the similarity of interventions	2	2	2	2
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	2	2-3	2	2
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A		N/A	N/A
Results						
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	2	2-3	3	3
	13b	For each group, losses and exclusions after randomisation,together with reasons	2	3	3	4
Recruitment	14a	Dates defining the periods of recruitment and follow-up	No	No	2	No
	14b	Why the trial ended or was stopped	3	2-3	2	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	2	3	4	4
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	2	3	4	4
Outcomes and estimation	17a	For each primary and secondary outcome, results for eachgroup, and the estimated effect size and its precision (such as 95% confidence interval)	2-3	3	4	3-5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	3			
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	3	3	N/A	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	3	3-4	4	6
Discussion						
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3-4	4-5	6	7
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	3-4	4-5	6	7
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	3-4	4-5	5	7
Other information						
Registration	23	Registration number and name of trial registry	4	No	No	No
Protocol	24	Where the full trial protocol can be accessed, if available	4	No	No	No
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Not mentioned	1	No	No
Total (n/25)			22	22	22	21

Table 3
Cochrane Risk of bias assessment tool.

Bias risk	Mardani et al. [9]	Adam et al. [10]	Bang et al. [11]	Spence [12]
Random sequence generation	Low risk	Low risk	Unclear risk	Low risk
Allocation concealment	Low risk	Low risk	Low risk	High risk
Blinding of participants and personnel	Low risk	Low risk	Low risk	Low risk
Blinding of outcome assessment	Low risk	Low risk	Low risk	Low risk
Incomplete outcome data	High risk	Low risk	High risk	High risk
Selective reporting	Low risk	Unclear risk	Unclear risk	Unclear risk
Other bias	Low risk	Low risk	Low risk	Low risk

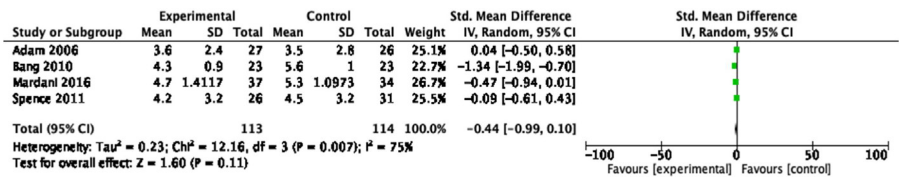

Fig. 2. Forest plot for post-operative pain.

and post-operative day 2 (gabapentin group, 4.26 [SD:2.39], vs control group, 4.03[SD:2.34]; $p = 0.71$) were comparable ($p > 0.05$). All studies but one reported the VAS score for pain. Spence et al used the Verbal Response Numerical Scale (VRNS) and because this is also scored 0-10 it was deemed appropriate to include it in the meta-analysis. Pooled data analysis did not demonstrate a significant beneficial effect of using gabapentin for postoperative pain control ($p = 0.11$), as shown in Fig. 2.

5. Opioids consumption

Three randomised controlled trials [9,11,12] assessed opioid consumption in the postoperative period. Mardani et al. [9] found significantly lower opioid consumption in the Gabapentin group. The pethidine consumption was lower in the gabapentin group at 6 hours (20.5 vs 40.3) and 24 hours (18.4 vs 40), $p < 0.0001$. Bang et al. [11] reported that the consumption of fentanyl over a period of 24 hours and the time of first opioid administration was not different between the groups. Spence et al. [12] also reported that total morphine equivalents on post-operative day 1 (gabapentin group, 9.75 mg [SD:6.58] vs control group, 9.52 mg [SD:4.75], $p = 0.88$) and post-operative day 2 (gabapentin group, 9.21 mg [SD:6.66] vs control group 6.93 mg [SD:5.44], $p = 0.170$ were similar. The use of different opioids in the three studies in the postoperative period precluded data synthesis for meta-analysis.

Table 4
Concise details of included studies.

Study	Population	Intervention (s)	Comparator	Outcome	Results
Mardani et al. [9] $n = 71$	ASA I&II Adult aged 18-75 Arthroscopic shoulder stabilisation	600 mg gabapentin 2 hours pre-op GA Mean age 30 71% male	Placebo 2 hours pre-op GA Mean age 28 79% male	VAS Opioid consumption Side effects	No significant difference in pain at 6 and 24 hours post-op ($p > 0.05$) Opioid consumption lower in gabapentin group ($p < 0.0001$) PONV significant lower after gabapentin at 6 hours ($p = 0.001$) but not at 24 hours
Adam et al. [10] $n = 54$	ASA I&II Adult aged 18-60 Variety shoulder arthroscopic procedures	800 mg gabapentin 2 hours pre-op GA and ISB $n = 26$ Mean age 43 67% male	Placebo 2 hours pre-op GA and ISB $n = 28$ Mean age 47 64% male	VAS VRS PONV Dizziness Drowsiness	No significant difference in pain in first 48 hours PONV gabapentin 26% and control 58% Sleep disturbance gabapentin 70% and control 65% Similar opioid consumption
Bang et al. [11] $n = 46$	ASA I&II Arthroscopic cuff repair	300 mg gabapentin 2 hours pre-op GA PCA post-op Mean age 54 39% male	Placebo 2 hours pre-op GA PCA post-op Mean age 59 35% male	VAS Fentanyl consumption Side effects	VAS significantly lower at 2, 6 and 24 hours ($p < 0.05$) No difference in fentanyl consumption Nausea: gabapentin 26%, placebo 35% Vomiting: gabapentin 12%, placebo 4%
Spence et al. [12] $n = 57$	ASA I&II Adult aged 18-60	300 mg gabapentin 1 hour pre-op continuing for 48 hours GA and ISB Mean age 32 85% male	Placebo 1 hour pre-op continuing for 48 hours GA and ISB Mean age 32 Male 84%	VRNS Morphine consumption	No significant difference in pain scores on day 1 ($p = 0.58$) or 2 post-op ($p = 0.71$) Equivalent morphine consumption ($p = 0.17$) Dizziness gabapentin 26.9%, control 43.3% ($p = 0.2$)

ASA: American Society of Anaesthesiologist grading; GA: General anaesthesia; ISB: interscalene block; VAS: visual analogue score; VRS: verbal rating scale; PONV: post-operative nausea/vomiting; PCA: patient controlled analgesia; VRNS: verbal numeric rating scale.

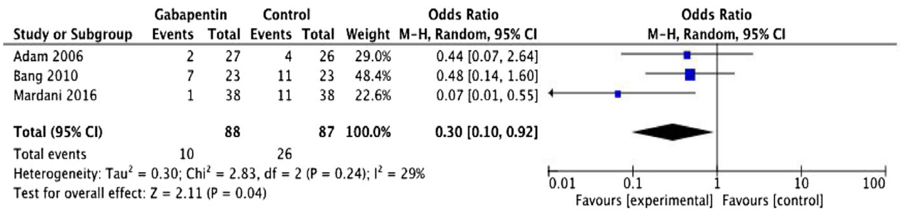

Fig. 3. Forest plot for post-operative nausea and vomiting.

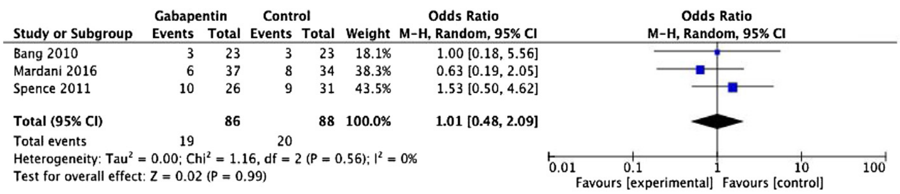

Fig. 4. Forest plot for postoperative dizziness.

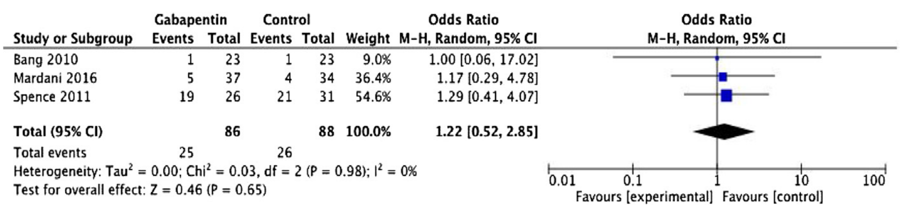

Fig. 5. Forest plot for postoperative drowsiness.

6. Nausea and vomiting

Three randomised controlled trials reported the incidence of nausea and vomiting after administration of either gabapentin or placebo. All three studies reported a lower rate of nausea and vomiting in the gabapentin group within the first 48 hours post-operatively. Mardani et al. [9] reported significantly lower nausea and vomiting in the gabapentin group at 6 hours postoperatively when compared to the placebo group (3% vs 32%, $p < 0.001$). However, Adam et al. [10] and Bang et al. [11] did not find the trend to be statistically significant. Meta-analysis of pooled data from the included studies revealed a significant beneficial effect of gabapentin in preventing nausea and vomiting in the post-operative period (OR 0.3, 95% CI 0.1 to 0.92), as shown in Fig. 3, with an unimportant level of heterogeneity between studies.

7. Dizziness and sedation

None of the included studies reported a significant difference between groups with respect to either dizziness or sedation. Mardani et al. [9] reported that the number of patients reporting dizziness was similar. At the 6 hours post-operatively, 6 patients (16%) in the gabapentin group and 8 patients (24%) inthe control group reported dizziness. At 24 hours post-operatively, 5 patients (14%) in the gabapentin group and 3 patients (9%) in the control group reported dizziness. The authors also report comparable sedation between the groups. Spence et al. [12] reported that there were no significant differences between the two groups in the frequency and severity of either dizziness or drowsiness within the first 48 hours ($p > 0.05$). Bang et al. [11] reported that the incidence of dizziness (13%) and drowsiness (4%) were equal in the gabapentin and placebo groups. Meta-analysis of data using 3 studies comparing dizziness and drowsiness failed to show any statistical significance as shown in Figs. 4 and 5.

8. Heterogeneity

Tau^2 was used to assess heterogeneity between studies, specifically the extent of variation among the effects observed (between study variance). For effects relating to dizziness and drowsiness Tau^2 was zero. For pain, and nausea and vomiting, this was 0.23 and 0.3 respectively. Caution should be applied in interpreting these values because it is well recognised that in small meta-analyses the number of studies included is often inadequate to accurately estimate heterogeneity. However, the main point to note is that heterogeneity between studies was not demonstrably high giving confidence that all included studies were evaluating the same outcomes and that pooling data in the meta-analysis was appropriate.

9. Discussion

The main findings of this study are that the use of gabapentin did not provide a significant benefit with respect to post-operative pain control but was associated with a significant reduction in postoperative nausea and vomiting after shoulder arthroscopy. Although all of the studies reporting this outcome showed a trend towards a reduction in nausea and vomiting with gabapentin, this did not achieve significance in two studies perhaps due to an inadequate sample size. One of the advantages of pooled data analysis is to improve statistical power by increasing the sample size and that was the main reason for conducting a meta-analysis. This demonstrated that gabapentin had a beneficial effect on post-operative nausea and vomiting in patients undergoing shoulder arthroscopy ($p = 0.04$). However, it should be noted that Mardani et al. [9] reported that the incidence of nausea and vomiting at 6 hours was significantly lower after gabapentin 3% vs 32% after placebo ($p = 0.001$). These findings are supported by a recent meta-analysis from Grant et al. which reported on patients undergoing a variety of surgical procedures [6] and demonstrated that pre-operative gabapentin was associated with a significant reduction in post-operative nausea and vomiting (risk ratio [RR] = 0.60; 99% confidence interval [CI], 0.50–0.72; $p < 0.0001$). This reduction in the incidence of post-operative nausea and vomiting after gabapentin has the potential to improve patient experience and reduce the number of readmissions follow day case shoulder arthroscopy [2,4].

In contrast, pooled data analysis of the included studies did not demonstrate a beneficial effect of gabapentin in preventing postoperative pain in shoulder surgery ($p = 0.11$). Mardani et al. [9] reported over 50% reduction in opioids consumption on the first post-operative day ($p < .0001$). Whilst Bang et al. [11] demonstrated a significantly lower VAS score after gabapentin administration up until 24 hours post-operatively. Previous studies have demonstrated that post-operative pain is the most frequent reason for acute presentations and readmission after shoulder arthroscopy [2,4]. Therefore, it was important to evaluate the ability of gabapentin to reduce the amount of post-operative pain. However, three studies [9,10,12] failed to show any significant improvement in pain scores despite using higher doses of gabapentin than Bang et al. In addition, the overall improvement in VAS score in the pooled data analysis (0.44 (95% CI –0.99 to 0.10) was below the minimal clinically important difference for VAS pain score in post-operative patients previously reported by Myles et al. [15]. Consequently, there does not appear to be a useful role for gabapentin with specific respect to post-operative pain management in modern multi-modal pain strategies.

Concerns regarding the potential increase in side effects subsequent to pre-operative gabapentin administration are not supported by the reviewed studies. Three studies compared the presence of dizziness or drowsiness in the gabapentin group to that in the placebo group and all failed to demonstrate any significant difference between the groups [9,11,12]. The failure to show any difference could be related to the relatively small study numbers for this secondary outcome measure. However, the meta-analysis has the advantage of pooling data to increase the study power and the failure of the meta-analysis to show any difference between the groups (Figs. 4 and 5) suggests there is no increased incidence of side effects in the early post-operative period and this should not restrict the pre-operative use of gabapentin.

Appraisal of the included randomised controlled trials was performed with respect to the CONSORT statement. All four studies were shown to be compliant with scores ranging between 21 and 22 (maximum score 25) as illustrated in Table 2. Potential study bias was evaluated using the Cochrane Collaboration's tool for assessing risk of bias, as shown in Table 3 the majority of studies were deemed to have a low risk for the majority of bias categories. However, two potential areas for bias were identified; the risk from incomplete outcome data was not adequately addressed in three of four studies and secondly the failure of three studies to provide published protocols which may risk the selective reporting of outcomes. Additional limitations of the review are acknowledged. Gabapentin was not the only form of analgesia used in the studies, both the type and amount of intra- and post-operative analgesia varied. In two studies [10,12] all patients received interscalene blocks (ISB) whilst in the other two studies ISB were not utilised [9,11]. ISB has been shown to reduce pain scores, delay first analgesic use and decrease overall opioids requirements [16]. Both of the studies using ISB did not find any benefit of using gabapentin, therefore the failure of gabapentin could be contributed to lack of central sensitization due to nerve block resulting in inhibition of analgesic effect of gabapentin. The dosages and administration time of gabapentin were inconsistent. Two studies [11,12] used 300 mg gabapentin preoperatively, Mardani et al. [9] used 600 mg and Adam et al. [10] used 800 mg preoperatively. In addition, Spence et al. [12] also received gabapentin postoperatively as well with 300 mg on the night of surgery and then 300 mg twice a day for 48 hours. The studies used different opioids in the post-operative period as rescue analgesia which precluded meta-analysis for this outcome. Another limitation is the failure of any study to report any delays in discharge or re-admission secondary to poor pain control, nausea or vomiting.

10. Conclusion

Gabapentin is associated with significant reductions in post-operative nausea and vomiting after shoulder arthroscopy. However, it does not appear to confer any advantage with respect to pain control over other multi-modal pain management strategies.

Disclosure of interest

Professor Adnan Saithna and Dr Matt Daggett are consultants with Arthrex. The other authors declare that they have no competing interest.

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Author contribution

A. ul Huda and R Jordan performed the literature searches, appraised the articles and produced the manuscript.

M. Daggett and A. Saithna conceptualised and designed the study, revised the manuscript critically for important intellectual content, and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.otsr.2019.09.023.

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