Clonidine versus tramadol for post spinal anesthesia shivering

A meta-analysis of randomized controlled trials

Jinguo Wang, *MD, PhD,* ***Haixiao Zhao,*** *MD,* ***Yanhui Li,*** *MD, PhD,* ***Rui Wang,*** *MD,* ***Na Wang,*** *MD, PhD.*

ABSTRACT

الأهداف: مقارنة عقار الكلونيدين بالترامادول في السيطرة على الارتعاش بعد تخدير العمود الفقري.

المنهجية: أجري البحث في الأدبيات المحدثة حتى أغسطس 2020م وأدرجت في هذه الدراسة التجارب المعشاة ذات الشواهد التي تقارن عقار الكلونيدين والترامادول للسيطرة على الارتعاش بعد تخدير العمود الفقري.

النتائج: وجدنا 14 دراسة مع 960 مريض. أظهر عقار الكلونيدين معدل أقل فعالية بالسيطرة على الارتعاش (OR: 0.59؛ 95% فترة الثقة: 0.40–0.88؛ p=0.009؛ I^2=36%)، ولكن مع انخفاض معدل حدوث الغثيان والقيء والدوخة. زاد عقار الكلونيدين من معدل حدوث بطء القلب وانخفاض ضغط الدم والتخدير مقارنة بعقار الترامادول.

الخلاصة: اظهرت الدراسة أن عقار الترامادول له فعالية أكثر في السيطرة على الارتعاش بالمقارنه مع عقار الكلونيدين، ولكنه يرفع معدل حدوث الغثيان والقيء والدوخة.

Objectives: To compare clonidine with tramadol for shivering control following spinal anesthesia.

Methods: The literature was searched updated to August 2020, and only randomized controlled trials comparing clonidine and tramadol for shivering control following spinal anesthesia were eligible for this study.

Results: Fourteen studies with 960 patients were identified. Clonidine demonstrated a lower effective rate of shivering control (OR: 0.59; 95% CI: 0.40-0.88; p=0.009; I^2=36%), but with decreased occurrence of nausea, vomiting, and dizziness. Clonidine increased the occurrence of bradycardia, hypotension, and sedation compared to tramadol.

Conclusion: Tramadol is more effective for shivering control than clonidine, but with increased occurrence of nausea, vomiting, and dizziness.

PROSPERO No: CRD42020207979

Keywords: shivering, spinal anesthesia, clonidine, tramadol

Saudi Med J 2021; Vol. 42 (4): 363-362
doi: 10.15537/smj.2021.42.4.20200342

From the Department of Urology (Wang J, Zhao); from the Department of Anesthesiology (Li, Wang N), The First Hospital of Jilin University; and from the Engineering Department (Wang R), Jilin Business and Technology College, Changchun, China.

Received 7th October 2020. Accepted 26th January 2021.

Address correspondence and reprint request to: Dr. Na Wang, Department of Anesthesiology, The First Hospital of Jilin University. Changchun, China. E-mail: wang_na@jlu.edu.cn
ORCID ID: https://orcid.org/0000-0002-8312-9787.

Shivering frequently occurs in the perioperative period.[1] Various medications have been studied for shivering control, including dexmedetomidine, clonidine, pethidine, tramadol, magnesium sulphate, dexamethasone, and ketamine.[2] Despite availability of numerous drugs for shivering control, no single drug has been found to be effective without any side effects.

In recent years, increasing randomized controlled trials (RCTs) comparing clonidine with tramadol for shivering control following spinal anesthesia have been conducted. Hence, we conducted this meta-analysis to compare clonidine with tramadol for shivering control following spinal anesthesia.

Methods. The recommendations of the PRISMA guidelines were followed in this meta-analysis.[3] We

searched Pubmed, Embase, Cochrane library, and Google Scholar, updated to August 2020 without language restrictions. All databases were searched using the following terms: "shivering," "clonidine," "tramadol," "hypothermia," "spinal anesthesia," "intrathecal injection," or "subarachnoid anesthesia." The references of all included articles were manually scanned for additional relevant publications.

Inclusion criteria were as follows: i) the study design is an RCT; ii) the participants were adult patients undergoing surgeries under spinal anesthesia; iii) the intervention of the study involved treating shivering following spinal anesthesia with intravenous clonidine or tramadol. The exclusion criteria were as follows: i) the study is not an RCT; ii) animal studies, meeting papers, editorials, correspondence, case reports or review papers; iii) and the intervention of the study includes clonidine or tramadol combined with other medications for shivering treatment.

The quality of the eligible RCTs were independently assessed by NW and HZ. Study quality was assessed with the Jadad score and the Cochrane risk of bias tool.[4,5] Disagreement was solved by JW. The data from each eligible RCT was separately extracted by JW and YL. Disagreement was also settled by RW. The following data were obtained from each eligible article: number of patients, publication year, study interventions, effective parameters of shivering control (effective rate of shivering control and recurrence rate), and the related complications. The main outcome was the efficacy of shivering control, and the secondary outcome was the related complications (hypotension, bradycardia, sedation, nausea, vomiting, dizziness, dry mouth).

Statistical analysis. Review Manager 5.3 was used for statistical analysis. The efficacy of shivering control and the related complications were displayed by the odds ratio (OR) with 95% confidence intervals (CI). Heterogeneity was estimated by the value of I^2. If I^2 was less than 50%, data were analyzed utilizing the fixed-effect model, or the random-effects model. $P<0.05$ was statistically significant.

Results. Initially, we found 476 studies. After assessment, 22 full texts were included; however, 8 articles were excluded because they involved children or animals, or were non-RCTs or correspondences. Thus, 14 RCTs involving 960 patients were eligible for the present study.[6-19] (Figure 1) Table 1 displays the characteristics of the identified RCTs in details and shows that all included studies in this meta-analysis had moderate to high quality. A risk-of-bias overview is shown in Figure 2.

As shown in Figure 3A, 12 studies including 860 participants recorded the effective rate of shivering control, and clonidine was less effective than tramadol (OR: 0.59; 95% CI: 0.40-0.88; p=0.009; I^2=36%). The difference in shivering recurrence rate was not statistically significant between clonidine and tramadol (OR: 0.82; 95% CI: 0.52-1.31; p=0.41; I^2=36%). (Figure 3B)

The most common treatment-related complications were evaluated. Clonidine had higher incidences of hypotension (OR: 5.97; 95% CI: 2.76-12.91;

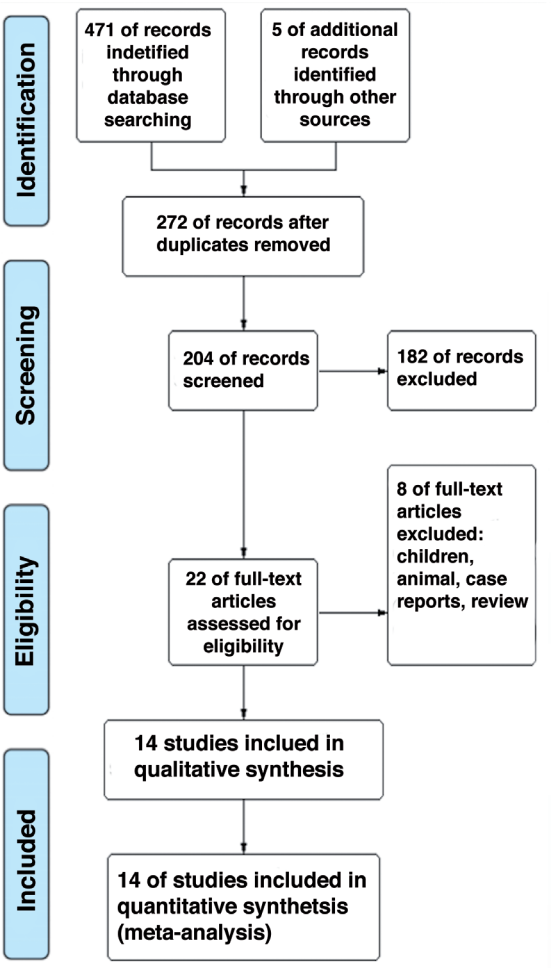

Figure 1 - Flow chart of selected randomized controlled trials.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Table 1 - Characteristics of the included trials.

Author/ date	Dosage	Study type	Jadad score	Sample size D/T	Patient characteristics; surgical setting	Type of anesthesia; drug for anesthesia	Degrees of shivering	Outcomes measures
Shukla et al[6] 2011	Clonidine 0.5μg/kg; tramadol 0.5 mg/kg	RCT	4	40/40	18-40 yr, ASA: I; Elective abdominal, orthopaedic and gynaecological surgeries	Spinal anesthesia; 0.5% bupivacaine 10-15 mg	Grades 3 or 4	1, 2 , 3 , 4, 5, 6, 7, 8
Vyas et al[7] 2018	Clonidine 1 μg/kg; tramadol 1 mg/kg	RCT	4	30/30	18-65 yr, ASA: I-II; Elective lower abdominal and lower limb surgeries	Spinal anesthesia; 0.5% heavy bupivacaine	Grades 1-4 for at least 2 minutes	1, 2 , 3 , 4, 5, 6, 7, 8
Venkatraman et al[8] 2018	Clonidine 1 μg/kg; tramadol 1 mg/kg	RCT	5	30/30	18-70 yr, ASA: I-II; Lower abdominal, lower limb, orthopaedic and plastic surgeries	Spinal anesthesia; No mention	Grades 2, 3 or 4	1, 2, 3, 4, 5, 6,
Bansal & Jain[9] 2011	Clonidine 150μg; tramadol 50 mg	RCT	4	30 /30	18-65 yr, ASA: I-III; Urological, inguinal, and lower limb surgeries	Spinal anesthesia; 0.5% heavy bupivacaine 3.2-3.5 mL	Grade 2 or 3	1, 2, 3, 5, 6,
Verma & Kumar[10] 2016	Clonidine 0.5μg/kg; tramadol 1.5 mg/kg (maximum 100mg)	RCT	3	30/30	18-45 yr, ASA: I-II; Elective abdominal, gynecological and orthopedic surgeries	Spinal anesthesia; 0.5% heavy bupivacaine 15 mg	Grade 2, 3 or grade 4	1, 2, 3, 4, 5, 6
Attal et al[11] 2015	Clonidine 50μg; tramadol 50 mg	RCT	3	30/30	18-40 yr, ASA: I-II; Elective lower abdominal and lower limb surgeries	Spinal anesthesia; 0.5% heavy bupivacaine 3.5 mL	Grade 3 or 4 for at least 2 minutes	1, 2 , 3 , 4, 5, 6, 8
Reddy & Chiruvella[12] 2011	Clonidine 50μg IV; tramadol 50 mg IV	RCT	4	45/45	18-35 yr, ASA: I-II; Elective or emergency caesarean section	Spinal anesthesia; 0.5% heavy bupivacaine 10 mg	Grade 3 or 4 for at least 3 minutes	1, 2 , 4, 5, 6, 8
Kulshrestha[13] 2014	Clonidine 50μg IV; tramadol 50 mg IV	RCT	4	45/45	18-35 yr, ASA: I-II; Elective Elective Lower Segment Caesarean Section	Spinal anesthesia; 0.5% bupivacaine 12mg	Grade 3 or 4 for at least 3 minutes	1, 2 , 3 , 4, 5, 6, 7, 8
Aravind et al[14] 2014	Clonidine 1 μg/kg; tramadol 1 mg/kg IV	RCT	4	40/40	18-40 yr, ASA: I-II; Various surgeries	Spinal anesthesia; 0.5% heavy bupivacaine	Grade 2, 3 or grade 4 for at least 2 minutes.	1, 2, 5
Longani et al[15] 2017	Clonidine 150μg IV; tramadol 50 mg IV	RCT	3	40/40	25-50 yr, ASA: I-II; Elective lower stomach and lower appendage surgeries,	Spinal anesthesia; 0.5% bupivacaine 14 mg	Grade 3 or 4 for at least 2 minutes	1, 2 , 3, 4, 5, 8
Jois et al[16] 2016	Clonidine 0.5μg/kg IV; tramadol 0.5 mg/kg IV	RCT	4	40/40	25-50 yr, ASA: I-II; Lower abdominal and lower limb surgeries	Spinal anesthesia 0.5% heavy bupivacaine 2-4mL	Grade 3 or 4	1, 2 , 3 , 4, 5, 6, 7, 8
Singh et al[17] 2016	Clonidine 0.5μg/kg IV; tramadol 0.5 mg/kg IV	RCT	4	30/30	20-50 yr, ASA: I-II; elective lower abdominal, lower limb orthopaedic and gynaecological surgeries	Spinal anesthesia 0.5% heavy bupivacaine 15 mg	Grade 3 or 4	1, 2 , 3 , 4, 5, 6, 8
Ali & Debata[18] 2017	Clonidine 50μg IV; tramadol 50 mg IV	RCT	3	30/30	18-60 yr, ASA: I-II; elective lower abdominal and lower limb surgery under spinal anesthesia	Spinal anesthesia 0.5% heavy bupivacaine	Grade 1, 2 or 3	2, 5
Kumar et al[19] 2016	Clonidine 0.6μg/kg IV; tramadol 1.0 mg/kg IV	RCT	3	20/20	18-60 yr, ASA: I-II; elective lower abdominal surgeries,orthopaedics lower limb surgeries and plastic surgeries.	Spinal anesthesia 0.5% heavy bupivacaine 15 mg	Grades 3 or 4	3

RCT: randomized controlled trial, ASA: American Society of Anesthesiologists, YR: year, IR: intravenous, Outcome measures: 1) Effective rate of shivering control, 2) Time to cease shivering, 3) Recurrent rate of shivering, 4) The incidence of bradycardia and hypotension, 5) The incidence of nausea and vomiting, 6) The incidence of sedation, 7) The incidence of dizziness, 8) The incidence of dry mouth

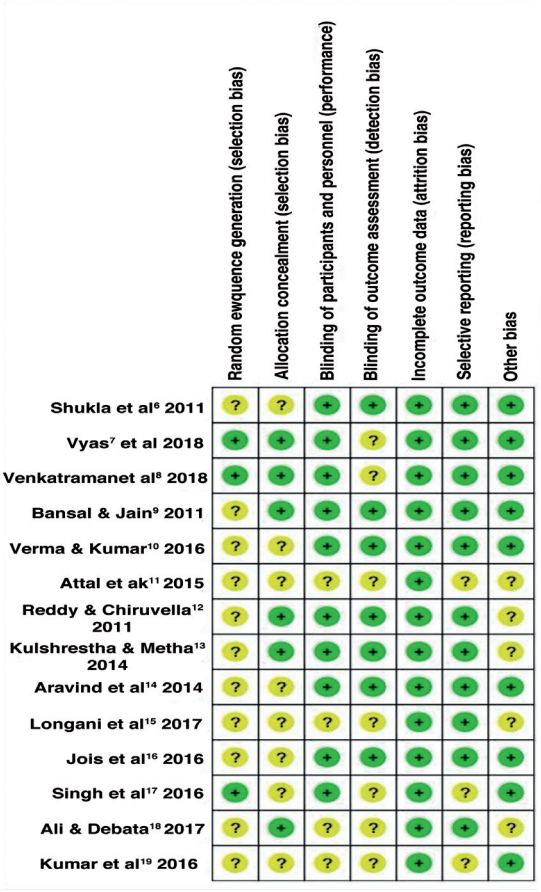

Figure 2 - Risk of bias evaluation.

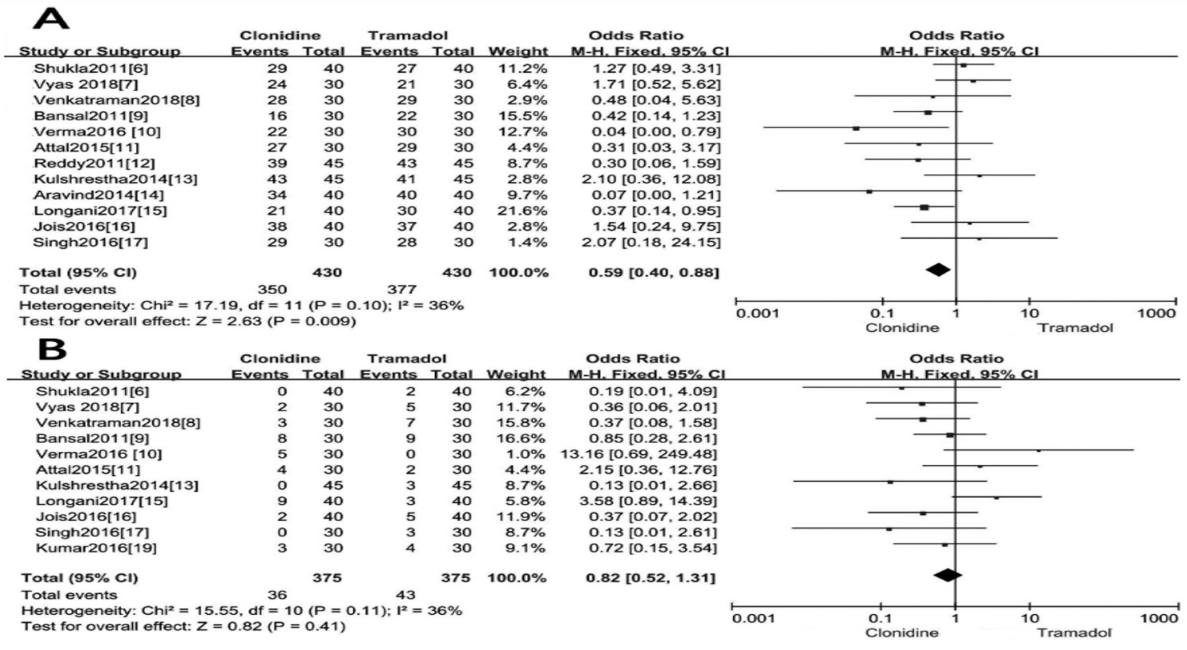

Figure 3 - **A**) Forest plot for effective rate of shivering control, **B**) and recurrent rate of shivering.

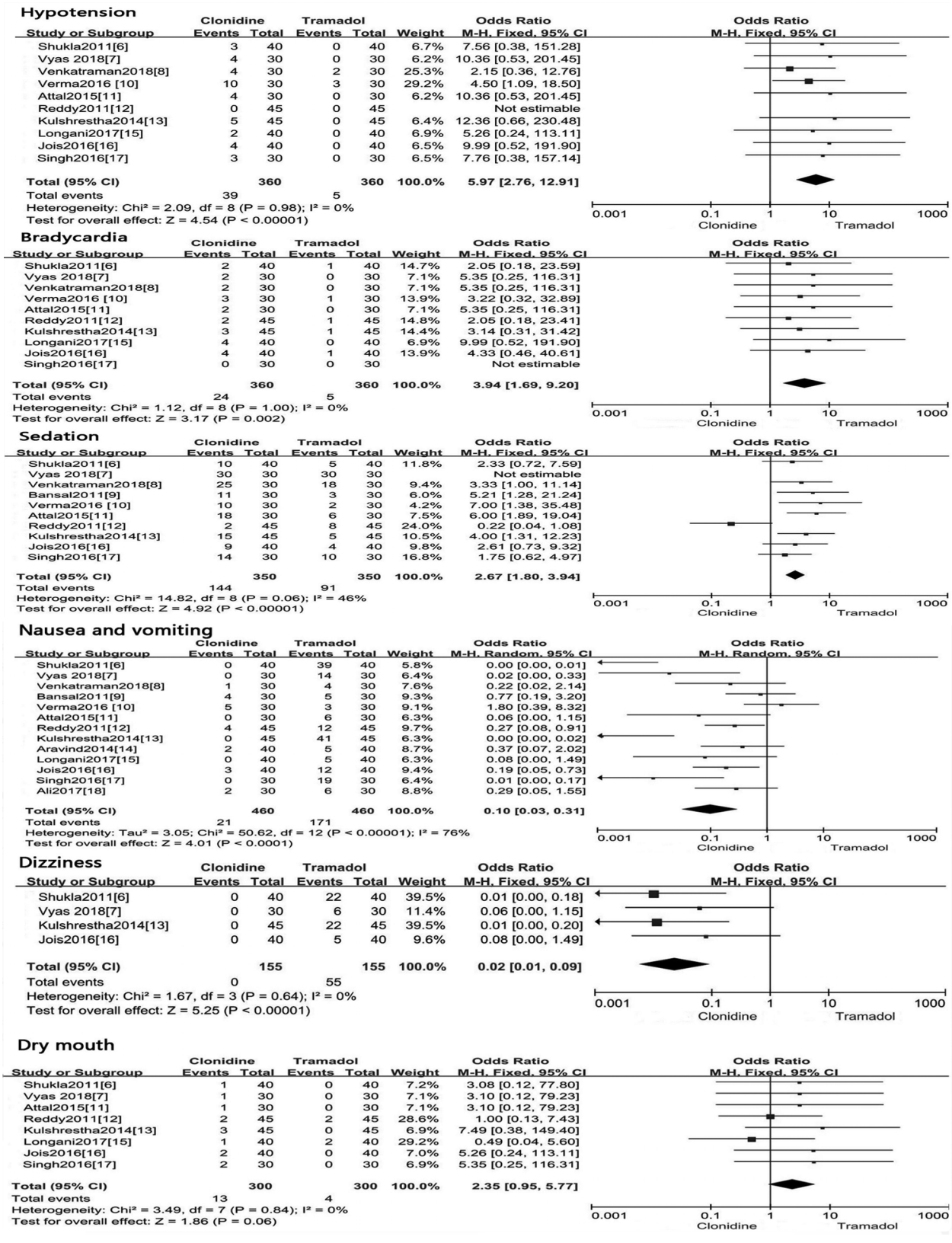

Figure 4 - Forest plot for related complications (hypotension, bradycardia, sedation, nausea, vomiting, dizziness, dry mouth).

p<0.00001; I^2=0%), bradycardia (OR: 3.94; 95% CI: 1.69-9.20; p= 0.002; I^2 = 0%), and sedation (OR: 2.67; 95% CI: 1.80–3.94; p<0.00001; I^2=46%), and lower incidence of dizziness (OR: 0.02; 95% CI: 0.01-0.09; p<0.00001; I^2=0%) compared with tramadol. (Figure 4)

Compared with tramadol, clonidine had a lower incidence of nausea and vomiting (OR 0.10; 95% CI: 0.03-0.31; p<0.0001; I^2=76%) (Figure 4). Sensitivity analysis was performed by taking out every included RCT sequentially. The result was confirmed, and no source of heterogeneity was identified.

The difference in the incidence of dry mouth was not statistically significant between clonidine and tramadol (OR: 2.35; 95% CI: 0.95-5.77; p=0.06; I^2=0%) (Figure 4).

The funnel plot of the effective rate of shivering control was symmetrical, so there were no potential publication biases.

Discussion. The present meta-analysis indicates that tramadol is more effective than clonidine for shivering control following spinal anesthesia. However, the difference is not significant in the shivering recurrence rate between clonidine and tramadol. In terms of complications, tramadol use resulted in higher incidences of nausea, vomiting, and dizziness, while clonidine increased the probability of bradycardia, hypotension, and sedation.

Nausea, vomiting, and dizziness are very distressing for patients and may lead to serious consequences.[20] According to the included RCTs, bradycardia and hypotension could be promptly treated by intravenous drugs. If surgeries are performed under spinal anesthesia, sedation caused by clonidine is beneficial for the patients. In addition, no patients were over sedated in the identified studies.

Clonidine has a high lipid solubility; therefore, it can promptly cross the blood-brain barrier.[21] Hence, clonidine can activate α2 receptors in the central nervous system to reduce the central thermosensitivity by suppressing the neuronal conductance, consequently reducing the thermoregulatory threshold for shivering.[21] The antishivering mechanism of tramadol possibly results from its opioid or serotonergic and noradrenergic function.[22]

Although the search strategy was designed to be as thorough as possible to identify eligible RCTs, the included RCTs were limited. Tramadol can significantly increase the effective rate of shivering treatment, but in terms of the complications, there is not enough clinical evidence to determine which of the 2, clonidine or tramadol, is better for shivering treatment after spinal anesthesia. Thus, further high-quality evidence from a large sample is needed.

In conclusion, tramadol is more effective than clonidine for shivering treatment, but with increased incidences of nausea, vomiting, and dizziness.

Acknowledgment. *The authors gratefully acknowledge Editage (www.editage.cn) for English language editing.*

References

1. Wang J, Wang Z, Liu J, Wang N. Intravenous dexmedetomidine versus tramadol for treatment of shivering after spinal anesthesia: a meta-analysis of randomized controlled trials. *BMC Anesthesiol* 2020; 20: 104.
2. Choi KE, Park B, Moheet AM, Rosen A, Lahiri S, Rosengart A. Systematic quality assessment of published antishivering protocols. *Anesth Analg* 2017; 124: 1539-1546.
3. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339: b2700.
4. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports on randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996; 17: 1-12.
5. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration. *BMJ* 2011; 343: d5928.
6. Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on post spinal anaesthesia shivering. *Indian J Anaesth* 2011; 55: 242-246.
7. Vyas V, Gupta R, Dubey P. Comparative efficacy and safety of intravenous clonidine and tramadol for control of postspinal anesthesia shivering. *Anesth Essays Res* 2018; 12: 663-668.
8. Venkatraman R, Karthik K, Pushparani A, Mahalakshmi A. A prospective, randomized, double-blinded control study on comparison of tramadol, clonidine and dexmedetomidine for post spinal anesthesia shivering. *Revista Brasileira de Anestesiologia* 2018; 68: 42-48.
9. Bansal P, Jain G. Control of shivering with clonidine, butorphanol, and tramadol under spinal anesthesia: a comparative study. *Local Reg Anesth* 2011; 4: 29-34.
10. Verma DNK, Kumar DM. Comparison of clonidine, dexmedetomidine and tramadol for control of post spinal shivering: A randomized double blind clinical study. *Int J Life Sci Scienti Res* 2016; 2: 658-664.
11. Attal P, Chhaya A, Singh T, Upadhayaya RM. Comparison of clonidine and tramadol for the control of shivering under spinal anaesthesia. *Int J Biomed* 2015; 6: 25-31.
12. Reddy VS, Chiruvella S. Clonidine versus tramadol for post spinal shivering during caesarean section: A randomized double blind clinical study. *J Obstet Anaesth Crit Care* 2011; 1: 26-29.
13. Kulshrestha S, Mehta RK. Efficacy of intravenous clonidine & tramadol on post spinal anaesthesia shivering in elective lower segment caesarean section: a randomized comparative study. *PJSR* 2014; 7: 7-11.

14. Aravind V, Dhakshinamoorthy M, Dhanasekaran C. A comparative study of clonidine and tramadol for the control of post spinal anaesthesia shivering. ***Int J Modn Res Revs*** 2014; 2: 379-384.
15. Longani S, Srivastava A, Bogra J, Agarwal A. A comparative study for control of shivering with clonidine, butorphanol and tramadol in patients undergoing neuraxial blockade. ***J Med Sci Clin Res*** 2017; 5: 29134-29139.
16. Jois DSM, Rao S, Krishna LS, Babu AS. A Prospective, randomized, double blinded, comparative study of clonidine and tramadol for control of shivering under spinal anesthesia. ***J Med Sci Clin Res*** 2016; 4: 11913-11921.
17. Singh A, Gupta KK, Solanki SL, Kumar M. A prospective randomized double blind comparative study of clonidine, dexmedtomidine and tramadol for treatment of shivering under spinal anaesthesia. ***Indian J Public Health*** 2016; 7: 114-119.
18. Ali SM, Debata PC. Comparative effectiveness of tramadol, clonidine & butorphanol for the control of shivering in patients undergoing neuraxial blockade. ***Int J Med Res Prof*** 2017; 3: 124-129.
19. Kumar YD, Kumar TR, Sasi RK. Prachi P. A clinical comparative study of dexmedetomidine, clonidine and tramadol in post spinal shivering in lower limb and lower abdominal surgeries. ***J Med Dent Sci*** 2016; 15: 50-54.
20. Weibel S, Rücker G, Eberhart LH, Pace NL, Hartl HM, Jordan OL, et al. Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis. ***Cochrane Database Syst Rev*** 2020; 10: CD012859.
21. Sanchez Munoz MC, De Kock M, Forget P. What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials. ***J Clin Anesth*** 2017; 38: 140-153.
22. Barakat A. Revisiting tramadol: A multi-modal agent for pain management. ***CNS Drugs*** 2019; 33: 481-501.