

Efficacy of dexmedetomidine for pain management in knee arthroscopy

A systematic review and meta-analysis

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Abstract

Background: Dexmedetomidine showed some potential in pain control in patients undergoing knee arthroscopy. We conducted a systematic review and meta-analysis to explore the efficacy of dexmedetomidine in patients undergoing knee arthroscopy.

Methods: We searched the randomized controlled trials (RCTs) assessing the effect of dexmedetomidine on knee arthroscopy in PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases. The primary outcome was pain scores. Meta-analysis was performed using the random-effect model.

Results: Five RCTs were included. Overall, compared with control intervention in patients with knee arthroscopy, dexmedetomidine intervention could significantly reduce the pain scores [Std. mean difference = -0.84 ; 95% confidence interval (95% CI) = -1.24 to -0.44 ; $P < .0001$] and postoperative diclofenac sodium consumption (Std. mean difference = -1.76 ; 95% CI = -3.32 to -0.21 ; $P = .03$), improve duration of analgesic effect (Std. mean difference = 1.78 ; 95% CI = 0.56 – 3.00 ; $P = .004$), but showed no influence on hypotension [risk ratio (RR) = 0.93 ; 95% CI = 0.14 – 5.92 ; $P = .94$], bradycardia (RR = 4.93 ; 95% CI = 0.91 – 26.58 ; $P = .06$), nausea, and vomiting (RR = 1.96 ; 95% CI = 0.31 – 12.58 ; $P = .48$).

Conclusion: Dexmedetomidine intervention was able to significantly reduce the pain scores and postoperative diclofenac sodium consumption, and improve duration of analgesic effect in patients undergoing knee arthroscopy, but had no influence on hypotension, bradycardia, nausea, and vomiting.

Abbreviations: CIs = confidence intervals, RCTs = randomized controlled trials, RRs = risk ratios.

Keywords: dexmedetomidine, knee arthroscopy, meta-analysis, pain management, systematic review

1. Introduction

Arthroscopic surgery was known as one of the most common orthopedic surgeries.^[1,2] However, irritation of free nerve endings in the synovial tissue, anterior fat pad, and joint capsule during arthroscopic excisions and resections would lead to varying levels of pain.^[3,4] Early mobilization and psychological state could be affected by postoperative pain, which could result in prolonged hospital stays and affects the prognosis adversely. Adequate pain relief was very important to reduce morbidity and promote postoperative recovery.^[5–7]

Intra-articular administration of drugs provided local analgesia with minimal systemic adverse effects.^[8,9] These drugs mainly included local anesthetics (e.g., lidocaine and bupivacaine), opioids (e.g., morphine and fentanyl), and $\alpha 2$ -agonists (e.g., clonidine) etc,

and they were found to achieve variable durations of analgesia.^[10–12] Dexmedetomidine was a highly selective, specific, and potent $\alpha 2$ -adrenergic receptor agonist, and had sedative, anxiolytic, analgesic, anti-hypertensive, and sympatholytic properties^[13–16] and showed some analgesic effect in arthroscopic surgeries.^[17] Many randomized controlled trials (RCTs) reported that dexmedetomidine was able to significantly reduce pain score and postoperative diclofenac sodium consumption, as well as improve duration of analgesic effect in knee arthroscopy.^[18–20]

In contrast to this promising finding, however, some relevant RCTs showed that dexmedetomidine had no influence on pain control and duration of analgesic effect in patients undergoing knee arthroscopy.^[17,21] Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of RCTs to evaluate the effectiveness of dexmedetomidine intervention on pain management in patients undergoing knee arthroscopy.

2. Materials and methods

This systematic review and meta-analysis was conducted according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement^[22] and the *Cochrane Handbook for Systematic Reviews of Interventions*.^[23] All analyses were based on previous published studies, and thus, no ethical approval and patient consent were required.

2.1. Literature search and selection criteria

PubMed, EMBASE, Web of Science, EBSCO, and the Cochrane library were systematically searched from inception to March 2017, with the following keywords

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dexmedetomidine, and knee arthroscopy or knee arthroscopic surgery. No limitation was enhanced. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly until no further article was identified. Conference abstracts meeting the inclusion criteria were also included.

The inclusion criteria were as follows: study population, patients undergoing knee arthroscopy; intervention, dexmedetomidine intervention; control intervention; outcome measure, pain score; and study design, RCT.

2.2. Data extraction and outcome measures

The following information was extracted for the included RCTs: first author, publication year, sample size, baseline characteristics of patients, dexmedetomidine, control, study design, pain score, postoperative diclofenac sodium consumption, duration of analgesic effect, hypotension, bradycardia, nausea, and vomiting. The author would be contacted to acquire the data when necessary.

The primary outcome was pain score. Secondary outcomes included postoperative diclofenac sodium consumption, duration of analgesic effect, hypotension, bradycardia, nausea, and vomiting.

2.3. Quality assessment in individual studies

The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis.^[24] This scale consisted of 3 evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). One point would be allocated to each element if they have been mentioned in article, and another 1 point would be given if the methods of randomization and/or blinding had been detailed and appropriately described. If methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then 1 point was

deducted. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score ≤ 2 was considered to be of low quality. If the Jadad score ≥ 3 , the study was thought to be of high quality.^[25]

2.4. Statistical analysis

Standard mean differences with 95% confidence intervals (95% CIs) for continuous outcomes (pain score, postoperative diclofenac sodium consumption, duration of analgesic effect), and risk ratios (RRs) with 95% CIs for dichotomous outcomes (hypotension, bradycardia, nausea, and vomiting) were used to estimate the pooled effects. All meta-analyses were performed using random-effects models with DerSimonian and Laird weights. Heterogeneity was tested using the Cochran Q statistic ($P < .1$) and quantified with the I^2 statistic, which described the variation of effect size that was attributable to heterogeneity across studies. An I^2 value greater than 50% indicated significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting 1 study in turn when necessary. Owing to the limited number (< 10) of included studies, publication bias was not assessed. $P < .05$ in 2-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics, and quality assessment

The flow chart for the selection process and detailed identification is presented in Fig. 1. Five hundred twenty-one publications were identified through the initial search of databases. Ultimately, 5 RCTs were included in the meta-analysis.^[17–21]

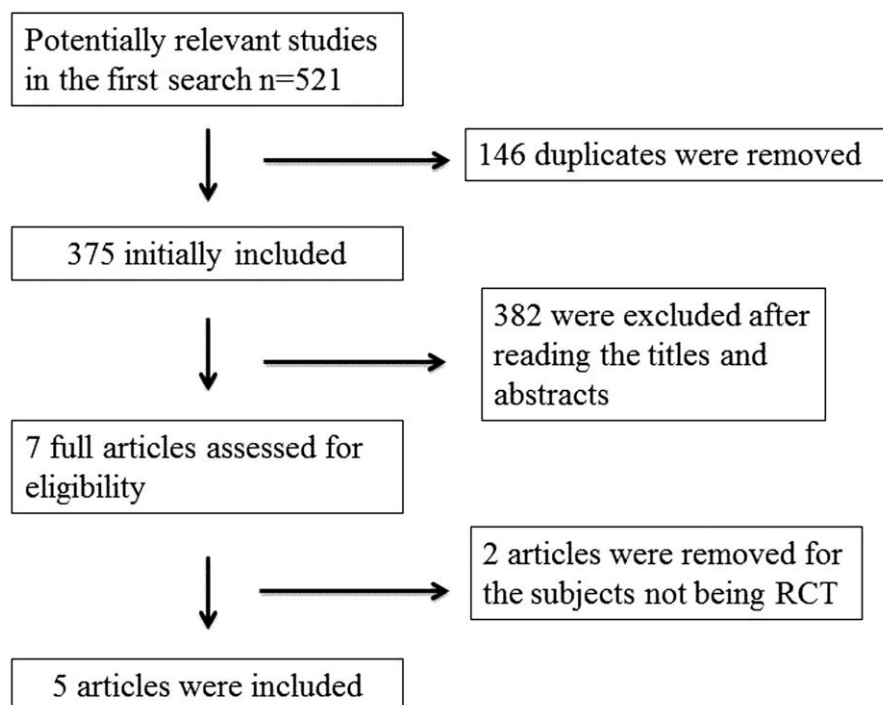


Figure 1. Flow diagram of study searching and selection process.

Table 1 demonstrates the baseline characteristics of the 5 eligible RCTs in the meta-analysis. The doses and methods of pregabalin were different in each RCT. They were intra-articular 18 mL ropivacaine, dexmedetomidine 2 µg/kg versus intra-articular ropivacaine (20 mL),^[20] intra-articular 100 µg (1 mL) of dexmedetomidine added to 19 mL of 0.25% ropivacaine versus intra-articular 19 mL of 0.25% ropivacaine and 1 mL of isotonic saline,^[19] intra-articular 1 µg/kg dexmedetomidine and isotonic saline versus intra-articular 25 mL isotonic saline,^[18] dexmedetomidine 1 µg/kg intravenously, for 10 minutes followed by dexmedetomidine 0.3 µg/kg for 50 minutes versus 2 g of propacetamol,^[17] and buccal dexmedetomidine 2.5 µg/kg versus buccal 0.9% NaCl 2 mL.^[21]

Among the 5 RCTs, 2 studies reported the pain score,^[18,19] 2 studies reported the postoperative diclofenac sodium consumption,^[20,21] 4 studies reported the duration of analgesic effect,^[18-21] and 2 studies reported the hypotension, bradycardia nausea, and vomiting.^[17,19] Jadad scores of the 5 included studies varied from 3 to 5; all 5 studies were considered to be high-quality ones according to quality assessment.

3.2. Primary outcome: pain score

These outcome data were analyzed with a random-effects model; the pooled estimate of the 2 included RCTs suggested that compared with control group, dexmedetomidine intervention was associated with a significantly decreased pain scores (Std. mean difference = -0.84; 95% CI = -1.24 to -0.44; *P* < .0001), with no heterogeneity among the studies (*I*² = 0%, heterogeneity *P* = .52) (Fig. 2).

3.3. Sensitivity analysis

No heterogeneity was observed among the included studies for the pain scores. Thus, we did not perform sensitivity analysis by omitting 1 study in each turn to detect the source of heterogeneity.

3.4. Secondary outcomes

Compared with control intervention, dexmedetomidine intervention showed significantly reduced postoperative diclofenac sodium consumption (Std. mean difference = -1.76; 95% CI = -3.32 to -0.21; *P* = .03; Fig. 3) and improved duration of analgesic effect (Std. mean difference = 1.78; 95% CI = 0.56-3.00; *P* = .004; Fig. 4), but had no increase in hypotension (RR = 0.93; 95% CI = 0.14-5.92; *P* = .94; Fig. 5), bradycardia (RR = 4.93; 95% CI = 0.91-26.58; *P* = .06; Fig. 6), nausea, and vomiting (RR = 1.96; 95% CI = 0.31-12.58; *P* = .48; Fig. 7).

4. Discussion

Our meta-analysis clearly suggested that compared with control intervention, dexmedetomidine intervention was associated with a significantly reduced pain score and postoperative diclofenac sodium consumption, improved duration of analgesic effect, but had no effect on hypotension, bradycardia, nausea, and vomiting.

Intra-articular injection of dexmedetomidine was reported to enhance postoperative analgesia after arthroscopic knee surgery, and reduce the need for postoperative analgesia.^[18] These analgesic effects relied on the direct local effect and central analgesic effect through the inhibition of transmission of painful stimuli in the posterior horn of the spinal cord. One previous study demonstrated that intra-articular dexmedetomidine

Table 1
Characteristics of included studies.

No.	Ref.	Dexmedetomidine group					Control group					Jada scores		
		Number	Age, y	Male (n)	Body mass, kg	Surgery duration, min	Methods	Number	Age, y	Male (n)	Body mass, kg		Surgery duration, min	Methods
1	Panigrahi et al ^[20]	20	32.3 ± 9.2	13	66.3 ± 6.9 kg	98.0 ± 29.0	Intra-articular 18 mL ropivacaine, dexmedetomidine 2 µg/kg	20	32.3 ± 9.2	14	63.6 ± 5.4 kg	93.0 ± 20.0	Intra-articular ropivacaine (20 mL)	4
2	Allpour et al ^[18]	21	30.8 ± 10.4	15	75.04 ± 9.9 kg	—	Intra-articular 1 µg/kg dexmedetomidine and isotonic saline	23	29.43 ± 9.3	17	75.52 ± 12 kg	—	Intra-articular 25 mL isotonic saline	5
3	Paul et al ^[19]	30	41.4 ± 12.8	21	56.32 ± 11.48 kg	80.44 ± 16.76	Intra-articular 100 µg (1 mL) of dexmedetomidine added to 19 mL of 0.25% ropivacaine	30	39.8 ± 12.6	22	54.35 ± 8.86 kg	77.56 ± 16.4	Intra-articular 19 mL of 0.25% ropivacaine and 1 mL of isotonic saline	4
4	Gomez-Vazquez et al ^[17]	15	36 (24-57)	—	78 (56-97) kg	55 (45-80)	Dexmedetomidine 1 µg/kg intravenously, for 10 min followed by dexmedetomidine 0.3 µg/kg for 50 min	15	30 (22-51)	—	78 (55-97) kg	55 (45-80)	2 g of propacetamol	3
5	Karastan et al ^[21]	21	44.1 ± 13.1	11	72.6 ± 18.2 kg	43.6 ± 11.0	Buccal dexmedetomidine 2.5 µg/kg	20	42.8 ± 14.0	10	72.6 ± 18.2 kg	42.4 ± 10.6	Buccal 0.9% NaCl 2 mL	3

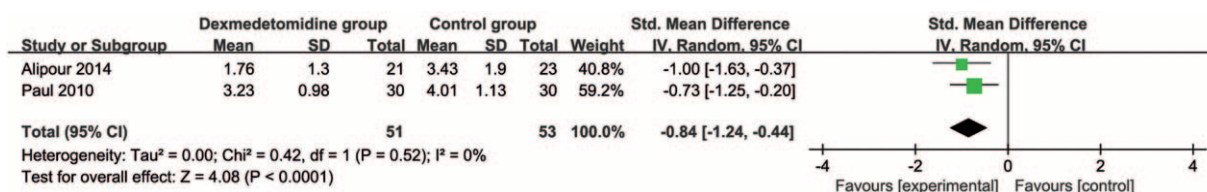


Figure 2. Forest plot for the meta-analysis of pain score.

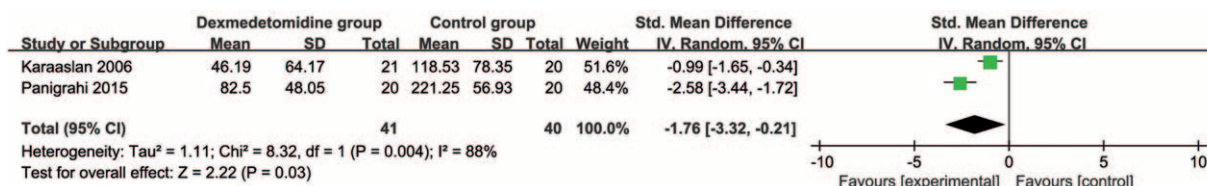


Figure 3. Forest plot for the meta-analysis of postoperative diclofenac sodium consumption (mg).

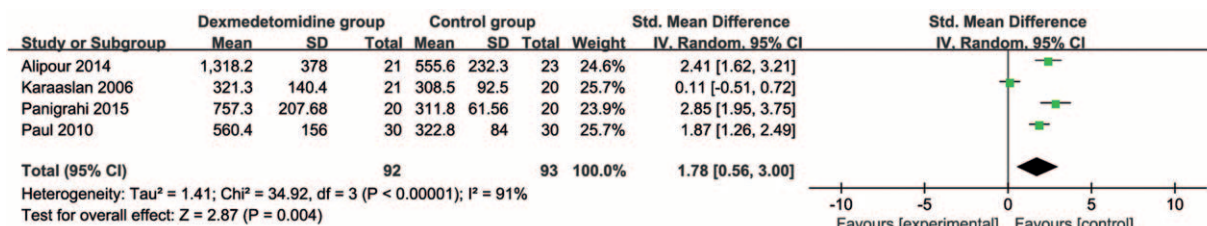


Figure 4. Forest plot for the meta-analysis of duration of analgesic effect (min).

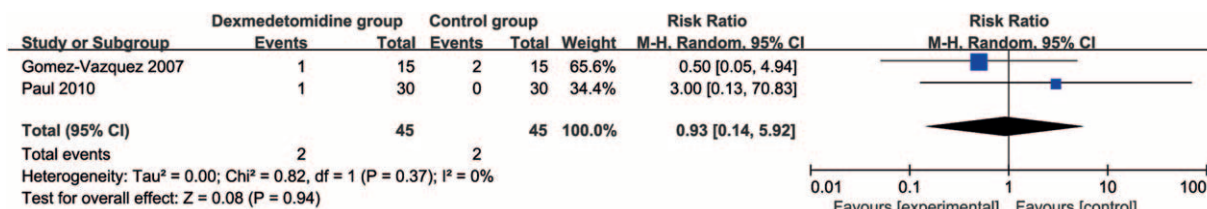


Figure 5. Forest plot for the meta-analysis of hypotension.

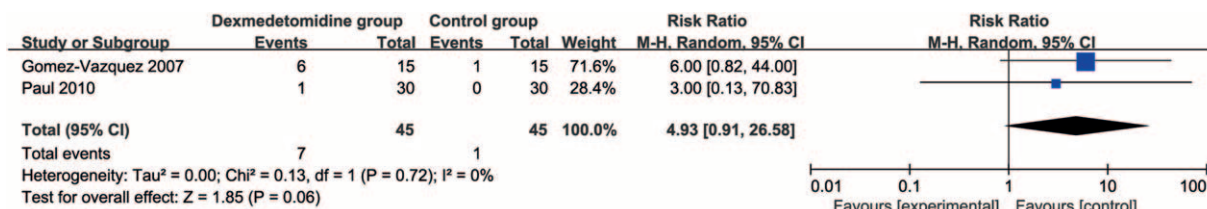


Figure 6. Forest plot for the meta-analysis of bradycardia.

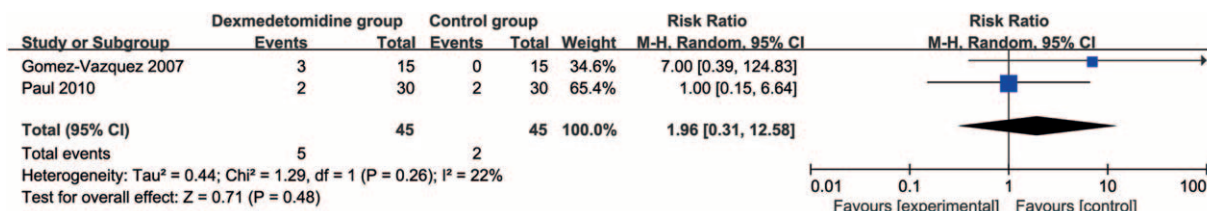


Figure 7. Forest plot for the meta-analysis of nausea and vomiting.

2 µg/kg and ropivacaine resulted in superior analgesic efficacy and better postoperative pain relief compared with intra-articular dexmedetomidine 1 µg/kg and ropivacaine following arthroscopic knee surgery, indicating the importance of dexmedetomidine concentration on analgesic effects.^[20] Furthermore, intra-articular analgesics benefited to knee mobilization, quadriceps exercise, and walking during functional recovery.^[20]

When analyzing duration of analgesic effect, there was significant heterogeneity among the 4 included RCT. After excluding 1 RCT using buccal dexmedetomidine, just low heterogeneity was found ($I^2=40\%$, heterogeneity $P=.19$).^[21] Three RCTs reported that intra-articular dexmedetomidine was able to significantly improve duration of analgesic effect compared with control intervention for arthroscopic knee surgery.^[18-20] However, the remaining 1 RCT showed that there was no significant difference of duration of analgesic effect between buccal dexmedetomidine and buccal 0.9% NaCl 2 mL.^[21] These results indicated that the analgesia effect of intra-articular dexmedetomidine was superior to that of buccal dexmedetomidine.

In addition, dexmedetomidine intervention was found to have no increase in adverse events including hypotension, bradycardia, nausea, and vomiting when compared with control group. One RCT reported that there were no significant differences of postoperative heart rate and mean arterial pressure between intra-articular dexmedetomidine 2 µg/kg and ropivacaine versus ropivacaine.^[20] However, a significant increase was noted in systolic, diastolic, and mean arterial pressures in patients receiving intravenous dexmedetomidine for several minutes compared with those patients getting propacetamol.^[17] Intra-articular dexmedetomidine might be better for the control of postoperative heart rate and mean arterial pressure than intravenous dexmedetomidine for arthroscopic knee surgery.

But there were several limitations. First, only 5 RCTs were included in our meta-analysis, and 5 of them had a relatively small sample size ($n < 100$). The doses and methods of dexmedetomidine in the included studies were different, and might have some impact on the pooled results. The volume of injected drug may increase the intra-articular pressure and excessive pressure may induce systemic absorption after the tourniquet was released.^[26] All included RCTs did not measure plasma concentrations of dexmedetomidine and correlate them with the clinical findings, which helped to confirm that the analgesia effect was local or systematic. Finally, the optimal dose and methods of dexmedetomidine for arthroscopic knee surgery remained elusive and required more clinical studies.

5. Conclusion

Dexmedetomidine showed an important ability to reduce pain and improve duration of analgesic effect in patients undergoing knee arthroscopy. Dexmedetomidine was recommended to be administrated for knee arthroscopy, but more studies should investigate its optimal dose and method.

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