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Review Article

Effect of clonidine on intraocular pressure following cataract surgery: a systematic review and meta-analysis

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Abstract: Background: Clonidine might be beneficial to the patients undergoing cataract surgery. However, the results remained controversial. We conducted a systematic review and meta-analysis to explore the effect of clonidine on intraocular pressure of patients undergoing cataract surgery. Methods: PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were systematically searched. Randomized controlled trials (RCTs) assessing the effect of clonidine versus placebo on cataract surgery were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. The primary outcome was intraocular pressure. Meta-analysis was performed using random-effect model. Results: Four RCTs involving 210 patients were included in the meta-analysis. Overall, compared with control intervention, clonidine intervention was found to significantly reduce intraocular pressure (Std. mean difference =-0.84; 95% CI=-1.18 to -0.49; P<0.00001) and improve Ramsay Scale (Std. mean difference =1.44; 95% CI=0.12 to 2.77; P=0.03), but showed no impact on heart rate (Std. mean difference =-0.38; 95% CI=-0.82 to 0.77; P=0.09) and arrhythmia (RR=0.32; 95% CI=0.03 to 3.84; P=0.37). Conclusions: Compared to control intervention, clonidine intervention was found to significantly reduce intraocular pressure and improve sedation, but showed no influence on heart rate and arrhythmia in patients undergoing cataract surgery.

Keywords: Clonidine, placebo, intraocular pressure, cataract surgery, meta-analysis

Introduction

Analgesia and ocular akinesia were required for performing cataract extraction [1, 2]. Phacoemulsification was known as the conventional method of cataract extraction with minimal perioperative and postoperative complications [3]. Transient elevation of intraocular pressure occurring 6-8 h after surgery was regarded as the most common postoperative complication [4] and resulted in more severe complications and consequences (e.g. central retinal artery occlusion, and postoperative ocular pain) [5]. The increase in intraocular pressure might be associated with trabecular meshwork edema and distortion due to surgical trauma, change in anterior segment angle caused by tightened surgical sutures, trabecular meshwork obstruction with cortical material, residual viscoelastic materials, and surgeon experience [6].

Clonidine was the prototype of alpha-2 agonistic adrenergic drugs with antihypertensive, sedative, and analgesic properties [7, 8]. Clonidine was found to make the eye surgery easy and reduce complications (e.g. expulsion of the vitreous humor) by decreasing intraocular pressure [9]. In addition, previous studies reported that clonidine could produce sedation without inducing hypnosis, and decrease postoperative pain, blood pressure and heart rate [10-12]. Previous studies reported that clonidine could significantly reduce intraocular pressure and promote sedation in patients undergoing cataract surgery [13, 14].

In contrast to this promising finding, however, some relevant RCTs showed that clonidine had no influence on heart rate and arrhythmia during laparoscopic cholecystectomy [15, 16]. Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of RCTs to evaluate the effect of clonidine intervention after cataract surgery.

Materials and methods

This systematic review and meta-analysis were conducted according to the guidance of the Preferred Reporting Items for Systematic Revi-

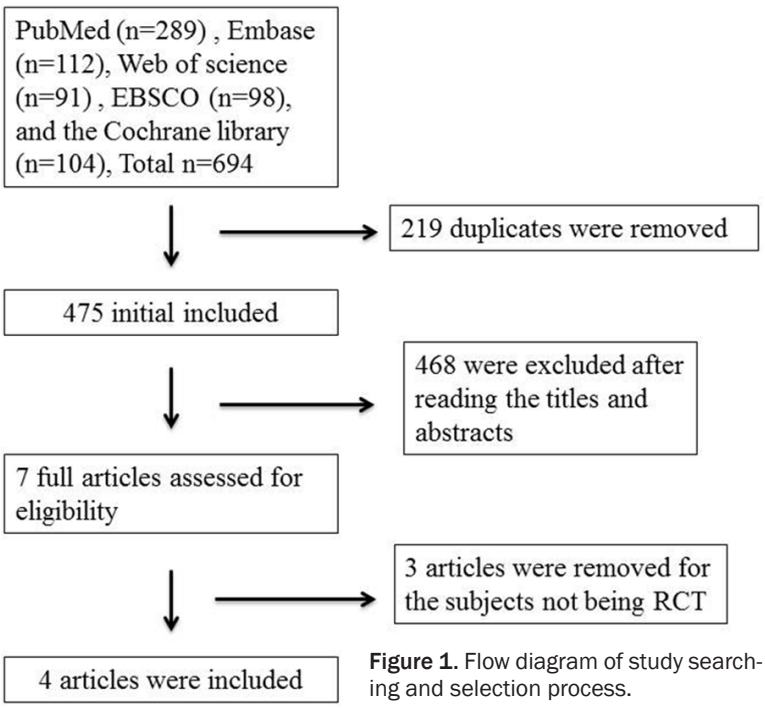

Figure 1. Flow diagram of study searching and selection process.

ews and Meta-analysis statement [17] and the *Cochrane Handbook for Systematic Reviews of Interventions* [18]. All analyses were based on previous published studies, thus no ethical approval and patient consent were required.

Literature search and selection criteria

PubMed, EMbase, Web of science, EBSCO, and the Cochrane library were systematically searched from inception to April 2017, with the following keywords: clonidine, and cataract. No limitation was enhanced. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also handsearched 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: (1) patients underwent cataract surgery; (2) Treatment intervention was clonidine versus placebo; and (3) study design was RCT.

The exclusion criteria included any history of ocular trauma and surgery, pseudoexfoliation syndrome, pigment dispersion syndrome, uveitis, and glaucoma.

Data extraction and outcome measures

The following information was extracted for the included RCTs: first author, publication year, sample size, baseline characteristics of patients, clonidine, control, study design, intraocular pressure, Ramsay Scale, heart rate, arrhythmia. The author would be contacted to acquire the data when necessary.

The primary outcome was intraocular pressure. Secondary outcomes included Ramsay Scale, heart rate, arrhythmia.

Quality assessment in individual studies

The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis [19]. This scale consisted of three 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 one point would be given if the methods of randomization and/or blinding had been detailedly and appropriately described. If methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then one 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 [20].

Statistical analysis

Standard Mean differences (Std. MDs) with 95% confidence intervals (CIs) for continuous outcomes (intraocular pressure, Ramsay Scale, heart rate), and risk ratios (RRs) with 95% CIs for dichotomous outcomes (arrhythmia) 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 ($P<0.1$) 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

Table 1. Characteristics of included studies

NO.	Author	Clonidine group					Control group					Jada scores
		Number	Age (years)	Male (n, %)	BMI (kg/m^2) or Body mass (kg)	Methods	Number	Age (years)	Male (n, %)	BMI (kg/m^2) or Body mass (kg)	Methods	
1	Santiago 2014	20	64.3±8.2	7 (35%)	65.8±10.7 kg	Intravenous clonidine 4 μg/kg	20	64.4±10.7	9 (45%)	70.0±13.1 kg	0.9% saline intravenously	5
2	Boroojeny 2012	31	64.19±7.59	18 (58.1%)	-	Preoperative oral clonidine (5 μg/kg)	31	66.12±8.03	18 (58.1%)	-	Matched placebo	4
3	Cruz 2009	20	61.5±16.4	13 (65%)	69.5±9.3 kg	Oral 100 μg clonidine	20	64±10.5	12 (60%)	63.7±9.5 kg	Matched placebo	3
4	Lemes 2008	33	63.42±15.34	13 (39.4%)	26.34±6.45 kg/m^2	Intravenous clonidine 2.5 μg/kg	35	69.11±10	13 (37.1%)	25.9±6.12 kg/m^2	Matched placebo	3

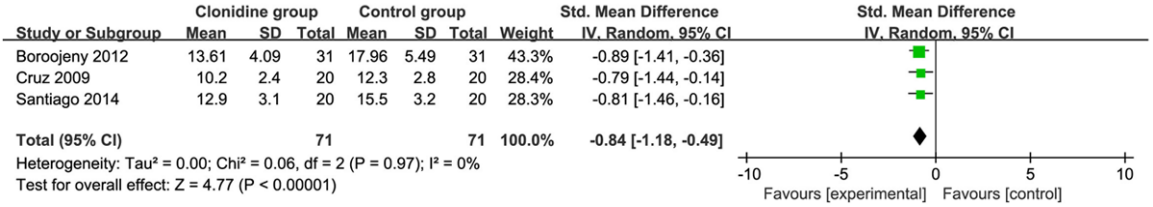

Figure 2. Forest plot for the meta-analysis of intraocular pressure, indicating that clonidine intervention had a reduced intraocular pressure than placebo treatment.

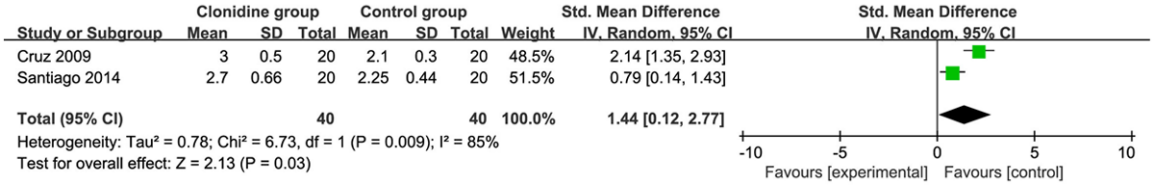

Figure 3. Forest plot for the meta-analysis of Ramsay Scale which was used to represent patient sedation, indicating that clonidine intervention had a improved sedation than placebo treatment.

of a single study on the overall estimate via omitting one study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias was not assessed. P<0.05 in two-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

The flow chart for the selection process and detailed identification was presented in **Figure 1**. 694 publications were identified through the initial search of databases. Ultimately, four RCTs were included in the meta-analysis [13-16].

The baseline characteristics of the four eligible RCTs in the meta-analysis were summarized in **Table 1**. The four studies were published between 2008 and 2014, and sample sizes ranged from 20 to 120 with a total of 210. There were no significant difference of age, body mass index (BMI) or body mass between clonidine group and control group at baseline. The methods of taking clonidine included oral and intravenous approaches. The doses of clonidine ranged from 2.5 μg/kg to 4 μg/kg, and one RCT reported patients with oral 100 μg clonidine.

Among the four RCTs, three studies reported the intraocular pressure [13-15], two studies reported the Ramsay Scale and heart rate [14, 15], and two studies reported the arrhythmia [15, 16]. Jadad scores of the four included studies varied from 3 to 5, all four studies were considered to be high-quality ones according to quality assessment.

Primary outcome: intraocular pressure

This outcome data was analyzed with the random-effects model, the pooled estimate of the three included RCTs suggested that compared to control group, clonidine intervention was associated with a significantly decreased intraocular pressure (Std. mean difference =-0.84; 95% CI=-1.18 to -0.49; P<0.00001), with no heterogeneity among the studies (I^2=0%, heterogeneity P=0.97) (**Figure 2**).

Sensitivity analysis

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

Secondary outcomes

Compared with control intervention, clonidine intervention showed significantly increase Ramsay Scale (Std. mean difference =1.44; 95%

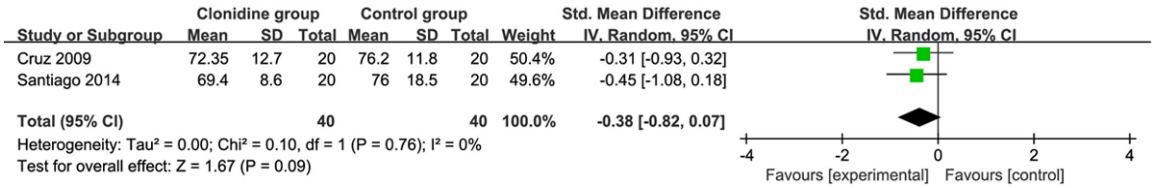

Figure 4. Forest plot for the meta-analysis of heart rate, indicating that there was no significant difference of heart rate between clonidine intervention and placebo treatment.

Figure 5. Forest plot for the meta-analysis of arrhythmia, indicating that there was no significant difference of arrhythmia between clonidine intervention and placebo treatment.

CI=0.12 to 2.77; P=0.03; **Figure 3**), but showed no influence on heart rate (Std. mean difference =-0.38; 95% CI=-0.82 to 0.77; P=0.09; **Figure 4**) and arrhythmia (RR=0.32; 95% CI=0.03 to 3.84; P=0.37; **Figure 5**).

Discussion

The sedative and anxiolytic effects of clonidine might avoid complications related to sympathetic stimulation because it acted through the binding to alpha-2 receptors [21, 22]. Reduced intraocular pressure during cataract extraction facilitated the surgery performance and reduced the risk of complications. And acute postoperative intraocular pressure rise after cataract surgery could cause central retinal artery obstruction and ischaemic optic neuropathy, optic nerve damage in glaucomatous eyes, and postoperative pain etc [23-25].

One RCT reported that 3 of 31 patients in clonidine group and 8 of 31 patients in control group suffered from acute rise in postoperative intraocular pressure. All 3 patients in clonidine group were controlled by one drug (Timolol maleate 0.5%, bid). In contrast, in placebo group, only 2 patients needed one drug (Timolol maleate 0.5%, bid) and other six patients required two drugs (Timolol maleate 0.5%, bid and oral Acetazolamide 250 mg qid) [13]. Our meta-analysis clearly suggested that clonidine intervention was associated with a significantly reduced intraocular pressure and improved sedation in patients with cataract surgery. In addition, clonidine was reported to significantly reduce pain during phacoemulsification, irrigation-aspiration and lens implantation [15].

Previous study showed that clonidine might have some ability to reduce the heart rate and blood pressure which was mediated by a decreased release of peripheral norepinephrine and a central sympatholytic effect [26]. Large dose of clonidine was found to reduce the blood pressure. Higher doses (300 μg) of clonidine was reported to result in bradycardia and hypotension [11]. However, there was no significant difference of heart rate between clonidine group and control group in this meta-analysis, possibly because the doses of clonidine for cataract surgery were relative small.

Clonidine might serve as an anxiolytic and anti-arrhythmogenic agent through inhibiting the sympathetic activity [27]. Arrhythmia before anesthesia was associated with the use of mydriatics and to anxiety. This meta-analysis showed no increase in arrhythmia was found after clonidine intervention in patient undergoing cataract surgery. Previous study reported that clonidine might have the ability to reduce the incidence of myocardial ischemia in patients with coronary heart disease [28]. In contrast, clonidine was found to have no effect on myocardial ischemia during cataract surgery [15].

Several limitations should be taken into account. Firstly, our analysis was based on four RCTs but all of them had a relatively small sample size (n<100). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples. More clinical trials with large sample were needed to explore this issue. The doses and methods of clonidine in the included studies were different and it probably affected the pooled results. Next, the optimal dose and duration of clonidine for cataract surgery remained unknown and required more clinical studies. Finally, some unpublished and missing data might lead bias to the pooled effect.

Conclusion

Clonidine showed an important ability to reduce intraocular pressure and improve sedation in patients undergoing cataract surgery. Clonidine was recommended to be administrated before cataract surgery.

Disclosure of conflict of interest

None.

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