Journal of Clinical Anesthesia 76 (2022) 110581

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Auricular stimulation for preoperative anxiety - A systematic review and meta-analysis of randomized controlled clinical trials

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ARTICLE INFO

Keywords:
Preoperative anxiety
Auricular stimulation
Transauricular vagal nerve stimulation
Systematic review

ABSTRACT

Study objective: Previous randomized controlled trials (RCTs) suggest that auricular stimulation (AS) is safe and effective in treatment of preoperative anxiety; however, a systematic evaluation is lacking. The aim was to summarize the evidence on efficacy and safety of AS for preoperative anxiety, as well as for other outcomes.
Design: We conducted a systematic review of RCTs including patients from all available populations. The search was done through MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Science and Scopus Database from inception to June 2020. Study selection and data extraction were performed in by 2 independent reviewers with ability to resolve disagreements by a third author. Meta-analyses as well as the risk of bias and evidence quality assessments were performed according to the Cochrane 6.2, 2021 handbook recommendations.
Interventions: We compared AS with pharmacological and non-pharmacological interventions for different outcomes.
Measurements: We assessed the repercussion of the evaluated interventions over anxiety scores and their safety, physiological parameters, perioperative medications requirement and intensity of postoperative pain.
Main results: We have included 15 studies with 1603 patients. AS has presented reduced anxiety scores as compared to the sham control (Standardized Mean Difference (SMD) -0.72, 95% confidence interval (CI) -1.09 to −0.36, $p < 0.0001$; 8 trials; 701 patients; heterogeneity: I^2 80%; GRADE: moderate certainty) and to no intervention (SMD -1.01, 95% CI -1.58 to −0.45, $p = 0.0004$; 4 trials; 420 patients; heterogeneity: I^2 84%; GRADE: very low certainty). There was no difference between AS and benzodiazepines (SMD -0.03; 95% CI: −0.34 to 0.28; $p = 0.84$; 3 trials; 158 patients; heterogeneity: I^2 0%; GRADE: very low certainty). No trials reported serious adverse effects of AS.
Conclusions: AS may be useful in treatment of preoperative anxiety. Due to heterogenous certainty in effect estimates, further research is needed to clarify the actual efficacy of AS for preoperative anxiety.

1. Introduction

Anxiety remains the most common burden of the perioperative experience reported by patients [1], appearing in more than 90% of adult patients, scheduled to elective surgery [2]. The high levels of preoperative anxiety are associated with an increased intensity of acute and persistent postsurgical pain, greater anesthetic requirement and impaired quality of life in the postoperative period [3–5].

Currently various psychological and pharmacological interventions are used to manage preoperative anxiety; however, none of them seems to be ideal in providing effective, safe and low-cost treatment [6–8].

Auricular stimulation (AS) is a method of complementary medicine, which may satisfy these criteria in treatment of preoperative anxiety [9]. AS, which includes auricular acupuncture and comparable techniques

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https://doi.org/10.1016/j.jclinane.2021.110581
Received 7 June 2021; Received in revised form 1 November 2021; Accepted 3 November 2021
Available online 12 November 2021

such as electroacupuncture and acupressure, is presumed to exert its anxiolytic effect *via* the stimulation of cranial nerves [10], modulating the brain areas involved in the stress response, such as the limbic system, locus coeruleus and hypothalamus [10–12].

In clinical setting, AS appeared to be safe [9,13] and superior to a variety of control conditions, as well as equally effective to benzodiazepines in reducing of anxiety scores in surgical patients [9,13–19]. However, these clinical investigations demonstrated a heterogeneity in regard to surgical procedures, control conditions and effect size, thus making it difficult to draw any definitive recommendations for clinical practice.

In order to address these limitations, we have performed the present systematic review and meta-analysis, which aimed to summarize the evidence and evaluate the effect size of AS on preoperative anxiety applied alone or in addition to standard care in comparison with various control conditions. The safety of AS, as well as the factors, that could have influenced the effects of this intervention, were also evaluated.

2. Methods

This systematic review was prepared in agreement with PRISMA guidelines [20]. The protocol of systematic review was registered with PROSPERO (CRD42020184795) and published elsewhere [21].

2.1. Search strategy

The search was done in following databases: MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Science, Scopus Database from their inception up to June 2020 according to PRISMA-S extension for reporting literature searches [22]. Various combinations of the following search terms were used: ‘randomized controlled trial’, ‘clinical trial’, ‘anxiety’, ‘fear’, ‘preoperative’, ‘surgical’, ‘intervention’, ‘anesthesia’, ‘auricular’, ‘ear’, ‘acupuncture’, ‘acupressure’, ‘electro-acupuncture’, ‘stimulation’. The details of complete search strategy are given in Appendix S1.

2.2. Eligibility criteria

We included randomized clinical trials with patients from any population undergoing medical interventions under any type of anesthesia - sedation, general anesthesia or locoregional anesthesia, comparing AS or related interventions (*e.g.*, auricular acupuncture, auricular acupressure, auricular electroacupuncture) with any type of pharmacological or non-pharmacological control interventions for anxiety scores, physiological parameters, perioperative medication requirement, safety of interventions and intensity of postoperative pain. We excluded those papers not reported in European languages.

2.3. Study selection

Researcher 1 (JD) and researcher 2 (KHu) imported eligible trials in an online review software “Covidence”, designed to conduct reviews according to Cochrane Collaboration standards [23]. Both researchers independently decided about trial inclusion. In case of conflicts a third researcher (TU) was involved in the discussion. When articles contained insufficient information to decide about eligibility, one of the researchers attempted to contact authors of the original reports to obtain further details *via* email. The details of data search and management are given as Fig. 1 and Appendices S1 and S2.

2.4. Data extraction

Data was extracted from the included trials according to the standardized form, designed by the review group (Appendix S2). Two researchers, MC and KHu checked completeness independently and entered data into Review Manager software (RevMan 5.3, 2011).

2.5. Outcome measures and data synthesis

Primary outcomes were patient-reported anxiety scales, such as the State Trait Anxiety Inventory (STAI), Anxiety Visual Analogue Scale-100 (VAS-100), the Amsterdam Preoperative Anxiety and Information Scale (APAIS) and Self-Rating Anxiety Scale (SAS). In case if an ordinal scale

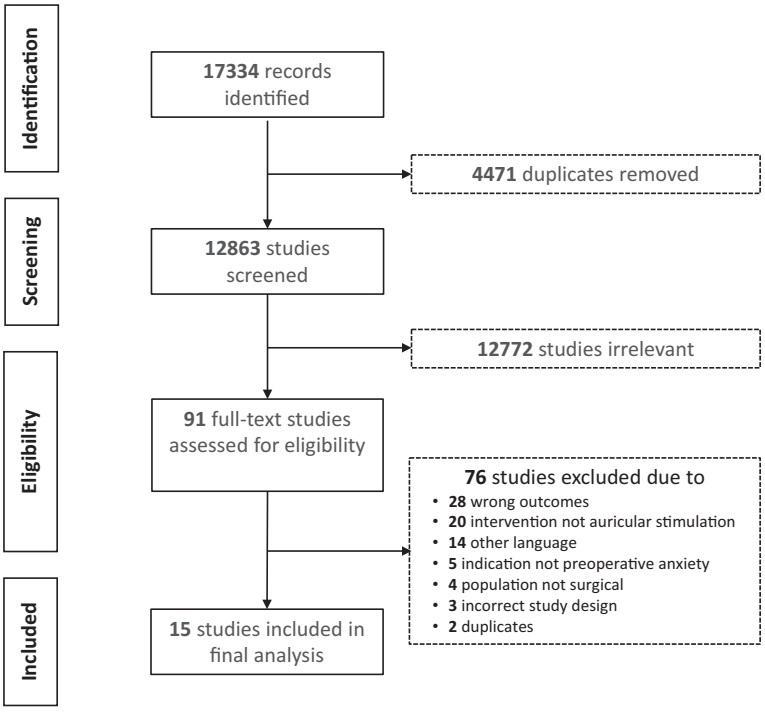

Fig. 1. PRISMA Flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

was used to measure preoperative anxiety, it was converted to a STAI (0–80) and VAS (0−10) scales. Each subject was assigned the appropriate STAI or VAS score according to the ordinal value provided. VAS-scales from 0 to 100 were recalculated to 0–10 for better comparison. Mean and standard deviation were calculated from the individual results for further data processing. Secondary outcomes included physiological parameters describing the response of the autonomic nervous system (*e.g.* heart rate, blood pressure, respiratory rate, sweating reaction); the intraoperative anesthetic requirement; the intensity of postoperative pain; the postoperative requirement for analgesic medication and patient satisfaction with the treatment of preoperative anxiety. Adverse event and serious adverse event reporting were analyzed, including events such as pain, inflammation and infection at the sites of auricular stimulation, and vasovagal reactions during the auricular interventions. Included data are presented as mean differences with 95% Confidence Intervals (CI), or as Standardized Mean Differences (SMD) with 95% CI. All outcomes were analyzed on an intention-to-treat basis. Trials with greater than 20% of missing data were excluded from the analysis.

Statistical analysis was performed with RevMan 5.3 (2011) software. Fixed-effect meta-analysis for combining data including primary outcome (anxiety scales) was calculated to estimate the treatment effect using SMD and 95% CI. Post-hoc trial sequential analysis (TSA) was performed on the primary outcome using the TSA Software from the Copenhagen Trial Unit, Centre for Clinical Intervention Research (Copenhagen) with a type I error of 5% and a power of 80%. *p*-values <0.05 were considered to be statistically significant.

2.6. Subgroup analysis and investigation of heterogeneity

Using RevMan 5.3 software, statistical heterogeneity was assessed in each meta-analysis using the T^2, I^2 and Chi^2 statistics. Heterogeneity was regarded as substantial if T^2 was greater than zero and either I^2 was greater than 50% or there was a low *p*- value (less than 0.10) in the Chi^2 test for heterogeneity. Where there was substantial statistical heterogeneity in pooled comparisons and one or more outlying trials, the outlier or outliers were excluded to test if heterogeneity was reduced and to see if the results were still consistent with an overall effect of the intervention. The GRADE tables were expanded to add additional rows where this was performed. We did not perform the other subgroup analyses as described in the protocol since there was no data found to allow such analyses.

2.7. Assessing risk of bias

Researcher 1 (JD) and researcher 2 (KHu) independently assessed the risk of bias for all included trials. Conflicts were resolved either by discussion or with a third researcher (TU).

According to the Cochrane Collaboration assessment RoB 2 tool the following 5 domains of bias were examined: i) bias arising from the randomization process; ii) bias due to deviations from intended interventions; iii) bias due to missing outcome data; iv) bias in measurement outcome; v) bias in selection of the reported result [24]. RoB was visualized using ROBVIS tool, described previously [25].

2.8. Certainty of outcome evidence

The certainty of outcomes was summarized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The certainty of pooled estimates was rated as high, moderate, low or very low.

3. Results

3.1. Characteristics of included trials

Out of 12,863 screened publications, 91 were selected and studied in full-text; 76 were excluded due to the reasons, listed at Fig. 1. Fifteen trials with 1630 patients were included in systematic review (Table 1), where 4 trials enrolled patients scheduled to dental treatment [16,19,26,27], one of them examining children [26], 2 trials reported on patients scheduled to otorhinolaryngology surgery [28,29], 2 trials included patients prior to lithotripsy [28,29], 3 trials on patients undergoing various ambulatory surgeries [15,19,32], 1 trial on patients prior to *in-vitro* fertilization [14], and another 3 trials on patients prior to gynecological [17], abdominal surgery [33] and cardiac catherization [34]. Among 1630 patients 67% were females. One trial did not provide information concerning gender [27]. The age of patients ranged between 10 and 77 years, the median was 39 years. All trials were performed in a hospital-based setting, except for three, 2 of which described surgery procedures in an outpatient clinic [16,19], and one which examined patients during prehospital transport [30]. Seven trials did not mention the funding source; 5 were investigator-sponsored, 2 obtained funding from the government and 1 received material from a company [17] (Appendix S3).

Nine trials had a two-armed design [17,27–34], 5 had a three-armed design [14–16,18,26] and one trial was four-armed [19]. Twelve trials used a sham control procedure, 3 trials compared AS with benzodiazepines [18,19,27]. Dellovo *et al* performed a crossover investigation, where patients received auricular acupressure and placebo midazolam during the 1st period of the study, and during the 2nd period they received midazolam and sham acupressure [27]. Karst *et al* (4 arms) compared auricular acupuncture to sham auricular acupuncture, midazolam and a no intervention group [19]. Lewis *et al* (3 arms) compared auricular acupressure with diazepam and with a relaxation technique [18]. Wu *et al* compared auricular with body acupuncture [32]. The details of study design and the characteristics of interventions are given in Appendix S4. Eight trials used unilateral [15,16,18,19,31,33,34] and 5 trials used bilateral AS [14,17,26,29,30]. Two trials did not give information about laterality of stimulation [27,32]. AS was applied using acupressure in 9 trials, acupuncture in 5 trials, one trial reported electrical stimulation for AS [28]. The most frequently used auricular points were MA-TF1 (*Shenmen*) ($n = 8$), MA-L (*Master Cerebral*) ($n = 6$), *Relaxation* point (n = 6), and *Tranquilizer* point ($n = 4$) (Appendix S5a). In 3 trials the point MA-TF1 (*Shenmen*) was used in combination with the body acupuncture point Ex-HN 3 [26,33,34]. Thus, these 3 trials were not included into subsequent meta-analysis. Auricular acupressure was performed with vaccaria seeds or plastic beads. One trial used a hand probe [29], another trial used a magnetic ball for acupressure [17]. Auricular acupuncture was performed using permanent either 0.2×1.5 mm needles or occlusive press needles. The duration of AS varied between 6 days and 10 min prior to a surgical procedure. The median of AS time was 30 min. Manual stimulation between 10 and 60 min was additionally applied in 6 trials [14,18,26,29,33,34], and 8 trials did not perform additional stimulation (Appendix S4). Wu *et al* used a continuous Self-Rating Anxiety Scale to measure the primary outcome [32]. Avisa *et al* used the Modified Child Dental Anxiety Scale faces version (MCDAS), a self-rating anxiety scale for children [26]. STAI scale was used to evaluate the primary outcome (preoperative anxiety) in 7 trials and VAS was used in 3 trials (Table 1). Three trials used Likert scales to evaluate preoperative anxiety [18,27,28].

3.2. Primary outcome: State anxiety

Four trials [26,32–34] were not included in the meta-analysis, because they used the scales, that could not be converted to STAI or applied therapeutic interventions additionally to AS: Wu *et al* randomized patients, scheduled to outpatient surgery either to auricular ($n = 18$) or body acupuncture ($n = 17$). Both interventions reduced anxiety, which was measured using the Self Rating Anxiety Scale. There was no difference between two study groups [32]. Another 3 trials were not included because they used the stimulation of the body acupoint Ex-HN3 in addition to auricular acupressure: Valiee *et al* performed either verum

Table 1
Characteristics of the trials included in systematic review.

First author, year (reference)	N of patients (female %)	Age (mean, years)	Surgery	Study intervention	Control intervention(s)	N of patients in		Anxiety assessment
						study group	control group(s)	
Avisa, 2018 [26]	375 (40)	11	dental	AuPrs	Sham/NI	125	250	MCDAS
Dellovo, 2019 [27]	30 (NR)	32	dental	AuPrs	Sham/Benz	30	30	4 point CDAS
Gol, 2020 [29]	66 (84)	30	ENT	AuPrs	NI	33	33	STAI
Karst, 2007 [19]	67 (45)	39	dental	AuPct	Sham/NI/Benz	19	48	STAI; VAS
Lee, 2013 [28]	50 (100)	48	ENT	AuES	Sham	25	25	5 point Likert scale
Lewis, 1987 [18]	90 (25)	40	various	AuPrs	RT/Benz	30	60	4 point Likert scale
Luo, 2016 [17]	43 (100)	36	gynecological	AuPrs	Sham	21	22	STAI
Mansoorzadeh, 2014 [34]	70 (45)	55	cardiac catherization	AuPrs	Sham	35	35	VAS
Michalek-Sauberer, 2012 [16]	182 (70)	38	dental	AuPct	Sham/NI	61	121	STAI; VAS
Mora, 2007 [30]	100 (65)	77	lithotripsy	AuPrs	Sham	50	50	VAS
Qu, 2014 [14]	305 (100)	32	IVF	AuPrs	Sham/NI	101	204	STAI; APAIS
Valiee, 2012 [33]	70 (64)	45	abdominal	AuPrs	Sham	35	35	VAS
Wang, 2001 [15]	91 (73)	40	various	AuPct	Sham	31	59	STAI
Wang, 2007 [31]	56 (60)	45	lithotripsy	AuPct	Sham	29	27	STAI
Wu, 2011 [32]	35 (60)	45	various	AuPct	BoPct	18	17	SAS

NR: not reported; ENT: ear nose throat surgery; IVF: *in vitro* fertilization; AuPrs: auricular acupressure; AuES: electrical stimulation of the auricle; AuPct: auricular acupuncture; NI: no intervention; Benz: benzodiazepines; RT: relaxation tape; BoPct: body acupuncture; MCDAS: Modified Child Dental Anxiety Scale (faces version); CDAS: Corah Dental Anxiety Scale; STAI: State Trait Anxiety Inventory; VAS: Visual Analogue Scale; APAIS: Amsterdam Preoperative Anxiety and Information Scale; SAS: Self-Rating Anxiety Scale.

or sham acupressure in 70 patients prior to various abdominal operations. Anxiety, respiratory rate and systolic blood pressure following the intervention were lower in the acupressure group as compared with the sham procedure [33]. Mansoorzadeh *et al* compared pre-procedural anxiety in 70 patients prior to cardiac catheterization and found that 35 patients who received verum acupressure reported less anxiety than the controls who received the sham procedure [34]. Avisa *et al* randomized 375 children prior to dental treatment into acupressure, sham and no intervention groups. Anxiety, which was measured using MCDAS, was lower in the acupressure group in comparison with the controls [26].

The meta-analysis of 11 RCTs, where anxiety levels were measured using STAI scale (or recalculated to STAI), revealed either equity or superiority of AS to an array of control conditions (Appendix S6).

In the analysis of 8 RCTs with 701 patients AS was superior to sham: SMD = −0.72, 95% CI (−1.09 to −0.36), $p < 0.0001$; (Fig. 2). Wang 2001 *et al* [15] compared sham procedure with 2 types (groups) of AS; the results of AS groups were summed up for this analysis. There was high heterogeneity among the trials ($I^2 = 80\%$). This heterogeneity was reduced ($I^2 = 44\%$) by exclusion of two outlying trials, and the result remained significant (Appendix S8).

AS was better than no intervention in all 4 RCTs with 420 patients, where anxiety was measured using STAI: SMD = −1.01, 95% CI (−1.58 to −0.45), $p = 0.0004$; (Appendix S7). There is high heterogeneity overall between the trials ($I^2 = 84\%$) in this analysis. Heterogeneity was eliminated by exclusion of the two outlying trials with the largest effect sizes, and the result was still significant (Appendix S8). Post-hoc trial sequential analysis confirmed evidence of the superiority of AS over sham controls and no intervention in the treatment of preoperative anxiety (Appendix S10).

The anxiolytic effect of AS, measured using STAI, was comparable with that of benzodiazepines in 3 trials with 158 patients: SMD = −0.03, 95% CI (−0.34 to 0.28), $p = 0.84$; (Fig. 3). There was no heterogeneity overall between the trials ($I^2 = 0\%$, Appendix S8).

3.3. Secondary outcomes

The heterogeneity of included trials regarding the secondary outcomes and lack of raw numeric data precluded the calculated summarization of secondary data. Three [26,27,33] out of 7 trials [17–19,26,27,30,33], monitoring heart rate (HR), reported on decreased HR following AS compared to the control condition. Regarding the blood pressure (BP) changes, one [33] out of 5 trials [17,18,27,30,33], monitoring BP, reported a reduction of BP after AS

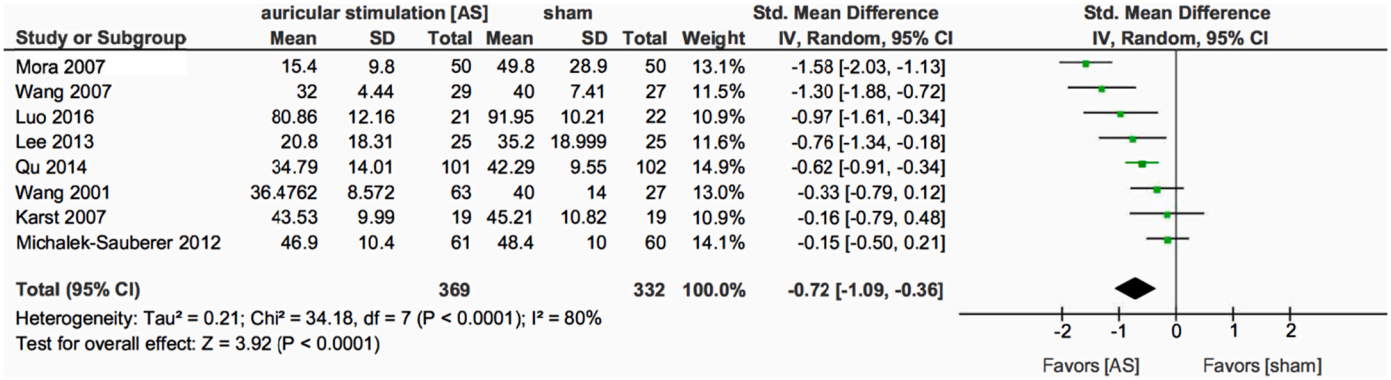

Fig. 2. Forest plot demonstrating the analysis of data from seven trials where auricular stimulation was compared with sham procedure. State anxiety was measured using State Trait Anxiety Inventory. SD: standard deviation; CI: confidence interval; AS: auricular stimulation.

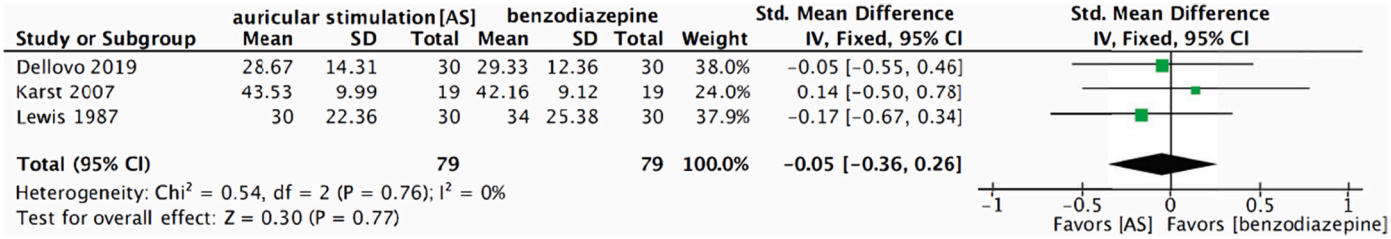

Fig. 3. Forest plot demonstrating the analysis of data from three trials where auricular stimulation was compared with benzodiazepines. State anxiety was measured using State Trait Anxiety Inventory. SD: standard deviation; CI: confidence interval; AS: auricular stimulation.

compared to the control group. One [27] out of 2 trials [28,29] examining serum cortisol, found the lower cortisol levels after AS *vs.* no intervention control, another one did not find a difference between auricular acupressure and no intervention regarding this parameter [28]. Further reported secondary outcomes were: oxygen saturation [19,27], ACTH [28] and blood glucose [29] levels, showing no differences after AS among the trial conditions. Valiee *et al* reported on decreased respiratory rate following AS compared with a sham control procedure [33] and Lewis described the lower incidence of palmar sweating in patients from the AS group in comparison with control conditions [18]. In the three-armed trial of Qu *et al*, where auricular acupressure was used to enhance the fertility in women undergoing IVF-oocyte retrieval, the authors reported a higher level of neuropeptide Y in the AS group compared with sham or no intervention [14].

Two trials evaluated intraoperative effects of AS: [17,31]. Luo *et al* reported lower Bispectral index values after auricular acupressure compared with a sham control [16] and Wang *et al* reported lower alfentanil requirement in the auricular acupuncture group compared with sham during a lithotripsy procedure [31]. Lee *et al* reported less postoperative pain in patients undergoing thyroidectomy who received auricular electric stimulation in addition to conventional pharmacologic analgesia compared with a sham procedure [28]. Patients' satisfaction was evaluated in 7 trials [16,18,19,26,27,29,31]. Patients from 3 trials were willing to choose auricular stimulation [18,26,30], whereas patients from another 4 trials rated auricular stimulation as good as control method [16,19,27,31].

3.4. Safety of the interventions

Six out of 15 trials reported on safety of the interventions [14,16,19,26,27,32]. No trial reported serious adverse effects of AS. Both auricular acupressure and auricular acupuncture elicited either no or mild side effects [16,19,27]. Dellovo *et al* reported one case (3%) of postoperative restlessness in the AS group compared with 27 (90%) in the midazolam group [27]. Karst *et al* reported that 37% of patients who received midazolam reported nasal burning, whereas 3 other trial arms reported no adverse effects [19]. Michalek-Sauberer *et al* reported a comparable incidence of side effects such as warmth or strange feeling at the treated ear or dizziness in both auricular acupuncture (14.2%) and sham procedure groups (12.2%) [16].

3.5. Quality assessment and risk of bias

Computer generated random sequence was used for randomization in 5 trials [16,17,27,28,31], the randomization method was not described in 3 RCTs [15,32,34], 2 trials used block randomization [26,29], 2 trials used a randomization list [14,19]. One trial used coin tossing [33] and another took the ends of the VAS scale to randomize the patients [30]. Two trials yielded the bias in the measurement of outcome [18,29] (Fig. 4). Overall low RoB was rated if only one domain had high RoB. The assessment of certainty of pooled outcomes using GRADE ranged from very low to high (Appendix S9): for comparison of AS *vs.* sham (8 trials) the certainty was moderate, but was very low for

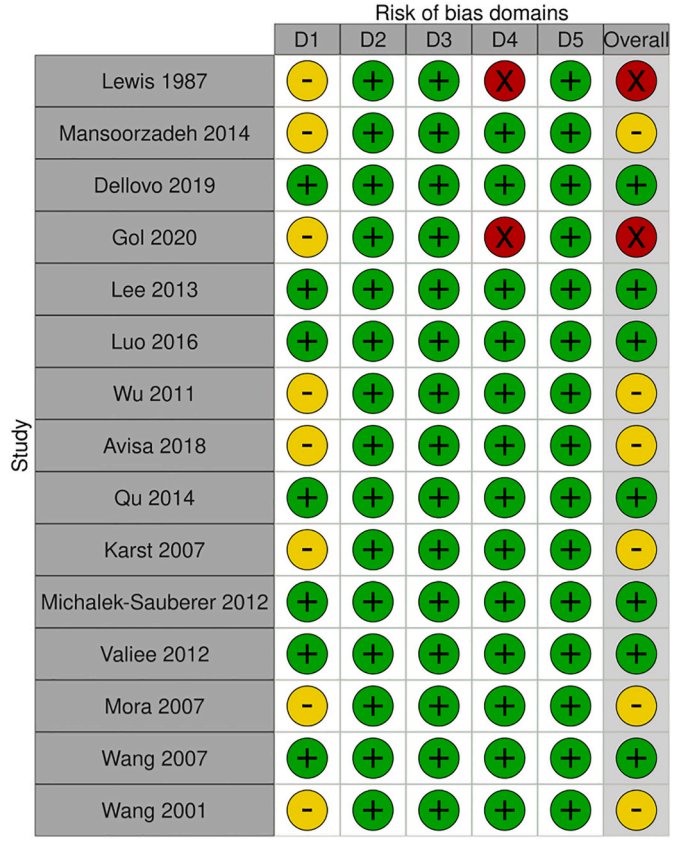

Fig. 4. Risk of bias summary for fifteen trials included in systematic review. Domains: D1: Bias arising from the randomization process; D2: Bias due to deviations from intended intervention; D3: Bias due to missing data; D4: Bias in measurement of the outcome; D5: Bias in selection of the reported result. : low risk of bias; : unclear risk of bias; : high risk of bias.

comparisons as *vs.* no intervention (4 trials) and AS *vs.* benzodiazepines (3 trials). Certainty increased for some comparisons in sensitivity analysis by excluding outlying trials.

4. Discussion

In this systematic review of randomized controlled trials on auricular stimulation (AS) applied to treat preoperative anxiety, AS was better in reducing of anxiety scores than sham and no intervention control

conditions and was comparable with conventional pharmacological anxiolysis using benzodiazepines. The effect size, calculated as Standardized Mean Difference between AS and sham control procedure was medium to large (0.72; Fig. 2), the certainty was moderate (Appendix 9), suggesting the clinical significance of this result. Although the effect size for the comparison of AS and no intervention was large (1.01; Appendix S.7), the certainty was very low. In the comparison of AS and benzodiazepines there was no significant or clinically relevant difference: SMD 0.03; 95% CI -0.34 to 0.28; Fig. 3), suggesting AS was not inferior to benzodiazepines, but it should be acknowledged that the certainty of evidence (GRADE) was very low (Appendix S9).

The low certainty of evidence, yielded by GRADE evaluation for comparisons AS *vs.* sham and AS *vs.* benzodiazepines is due to inability to mask personnel in 2 trials [18,29], resulting in high risk of bias in domane D4 (Fig. 4). The exclusion of the results of Gol et al. [29], in subgroup analysis, results in moderate certainty (GRADE) for the comparison of AS *vs.* no intervention (Appendix S9) due to an improvement in risk of bias and inconsistency. In acupuncture studies, the practitioner who delivers acupuncture, can rarely be blind to the intervention. However, in the present review 2 trials did successfully mask their practitioners. Mora *et al* [30] instructed paramedics, who were naïve to acupuncture, how to apply acupressure seeds telling them they would compare two equally active treatments. For sham stimulation in another trial, Lee *et al* used the same electrostimulation device, which was set to an inactive mode for the control condition [28]. However, these solutions represent rather an exceptional example in the practice of clinical acupuncture research, where the potential bias related to the inability to mask acupuncturists is addressed to some degree by ensuring patients' masking during and after the acupuncture procedure [35,36].

Three trials reported the comparable effect of AS and benzodiazepines on anxiety levels measured with STAI, but the drug interventions were associated with a higher incidence of unwanted side effects. These findings, regarding adverse events, support the results of recent rigorous placebo-controlled research of premedication using benzodiazepines on postoperative satisfaction and recovery, which demonstrated that the benefits of preoperative benzodiazepine use did not outweigh the risks and benefits [7,37].

The most frequently used points in these 15 trials were MA-TF1 (*Shenmen*), MA-L (*Master Cerebral*) and *Relaxation* acupoints. However, these 3 auricular acupoints were mainly used in combination with other auricular points or the body acupuncture point Ex-HN3 and the sample size was rather small, thus we cannot suggest that any of the auricular stimulation sites are better than any others for treatment of preoperative anxiety. Examining the location of all auricular stimulation sites (Appendix S5b) shows that almost all of them are situated in the areas of overlapping of auricular branch of the vagal nerve (ABVN), trigeminal nerve and great auricular nerve from the cervical plexus [38]. This is consistent with the current physiological view of the potential mechanisms of AS *via* ABVN and other cranial nerves with subsequent modulation of the brain areas involved in the stress response [10–12,38,39]. Neuroimaging studies showed that electrical stimulation of the auricular branch of the vagal nerve was associated with increased activation in the nucleus tractus solitaries (NTS), locus coeruleus, insula, thalamus und anterior cingulate cortex and decreased activation in limbic structures such as amygdala, hypothalamus, hippocampus and posterior cingulate cortex [11,40,41]. These cerebral regions are involved in anxiety and mood regulation *via* production of various neurotransmitters, including serotonin, dopamine, norepinephrine, GABA, and glutamate, that usually serve as pharmacological targets for anxiolytic medication [42–44]. The exact underlying anxiolytic mechanisms of AS are still to be elucidated.

The heterogeneous results of secondary outcomes confirm the current state of research, that so far there is no validated clinically relevant biomarkers of situational anxiety. The most promising and convenient biomarkers to be measured within the human model are probably heart rate variability, serum catecholamines and cortisol, as well as salivary alpha-amylase [45].

4.1. Comparison with other studies

Recently Tong *et al* evaluated the effect of acupuncture for treatment of preoperative anxiety, including the trials using both body and auricular acupuncture in a systematic review [46]. Out of 12 included RCTs with an overall low certainty of evidence, 6 were performed using body acupuncture. Six other trials used AS, 2 of them were included in our review [17,31], however Tong *et al* evaluated the risk of bias for these 2 trials lower than in our review. The authors concluded that acupuncture may reduce preoperative anxiety, but could not draw any definitive recommendation due to small sample sizes of the included trials. The results of our investigation also confirm the findings from the series of experimental trials on treatment of pre-exam anxiety using auricular acupuncture. Pre-exam anxiety, as well as preoperative anxiety, is a kind of situational anxiety, which terminates itself when the underlying condition (exam or surgery) is over. Thus, pre-exam anxiety is a convenient model to study the efficacy and mechanism of AS. In these series of trials AS (auricular acupuncture) was better than placebo procedure and better than several standard psychological methods in reducing of pre-exam anxiety and improving the quality of sleep in medical students [47–49]. The simultaneous changes of hemodynamic parameters and salivary alpha-amylase attributed these clinical effects to reduced activity of the sympathetic nervous system [48,49].

4.2. Safety

Overall, according to the reports of included trials, AS was a safe method, inducing only mild unwanted side effects such as local paresthesia or dizziness in less that 15% of patients. The absence of vasovagal reactions, which can occur in less than 5% of cases during auricular irritation [50], may be explained by increased sympathetic tone in patients before surgery. Also, the use of minimally invasive AS methods and devices (acupressure, transcutaneous electrical stimulation and short indwelling needles) during the short period of application prior to surgery precluded such unwanted side effects as infection resulting in chondritis and perichondritis, summarized in a recent systematic review [51].

4.3. Limitations

Despite the strict adherence of our systematic review to PRISMA and CONSORT statements, it has several limitations. Restricting the inclusion criteria only to the trials published in European languages, we have certainly introduced bias by excluding the reports from the countries of the Far East, where auricular stimulation is often used in traditional medicine [52]. For example, the systematic review of Tong *et al* [46] analyzed 4 trials on auricular acupuncture for preoperative anxiety from China, which we excluded according to language criteria from our investigation. Moreover, we did not evaluate the time expenditure, personnel and material costs for AS in our systematic review. This is required to further assess the options for implementation of AS in treatment of preoperative anxiety in clinical routine. In addition, the use the network meta-analysis approach, which we did not use in the present investigation, could have probably give more precise evaluation of the effects of various AS modalities.

5. Conclusion

All trials included in this systematic review demonstrated that auricular stimulation (AS) reduces preoperative anxiety. Subsequent meta-analysis and trial sequential analysis demonstrated that AS is superior to sham and no intervention and comparable to commonly used benzodiazepines in the treatment of preoperative anxiety. It seems that AS may be useful in treatment of preoperative anxiety, however the

clinical relevance remains unclear due to heterogeneous certainty in effect estimates. Further research is needed to clarify the actual efficacy of AS for preoperative anxiety.

CRediT authorship contribution statement

Taras I. Usichenko: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Kevin Hua:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Mike Cummings:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Andreas Nowak:** Project administration, Resources, Supervision, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Klaus Hahnenkamp:** Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Benno Brinkhaus:** Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Joanna Dietzel:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

Funding

This work was supported by internal funding of the Department of Anesthesiology, University Medicine of Greifswald and Institute for Social Medicine, Epidemiology and Health Economics, Charité University Medicine, Berlin. KHu and JD received each a research grant from the Karl and Veronica Carstens Foundation.

Declaration of Competing Interest

None declared.

Research data can be retrieved *via* Mendeley Data at: https://data.mendeley.com/datasets/88rfc9wm5m/1

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2021.110581.

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