Review Article

Efficacy and safety of oral tizanidine premedication as pre-emptive analgesia in adult patients undergoing elective surgeries- A systematic review

ABSTRACT

Tizanidine is a centrally acting α2 agonist which has been used as a premedication due to its opioid-sparing and sympatholytic properties. This systematic review assessed the safety and feasibility of oral tizanidine. After registering the protocol with PROSPERO (CRD42022368546), randomized controlled trials and non-randomized observational studies were searched in various databases. The primary outcome was intraoperative opioid use; the secondary outcomes were 24-hr opioid consumption, pain scores, time to rescue analgesia, and adverse events. The risk of bias scale was used to assess the quality of evidence. Out of 202 studies identified, five studies fulfilled the inclusion criteria. Intraoperative opioid consumption was significantly less in the tizanidine group (MD: -2.40; 95% CI: -4.22, -0.59; $P = 0.010$; $I^2 = 0$ %). The 24-hr opioid consumption was comparable between both groups (MD: -42.53, 95% CI: -91.45, 6.39; $P = 0.09$; $I^2 = 99\%$). Time to rescue analgesia was comparable between both groups (MD: 308.22; 95% CI: -263.67, 880.11, $P = 0.29$, $I^2 = 100\%$). Pain scores at 6 and 12 hours were comparable (MD: -1.37; 95% CI: -3.68, 0.94; $P = 0.24$; $I^2 = 97\%$) and (MD: -1.76; 95% CI: -4.06, 0.53; $P = 0.13$; $I^2 = 95\%$); however, at 24 hours the scores were better in the tizanidine group (MD: -1.10; 95% CI: -1.50, -0.69; $P < 0.0001$ $I^2 = 0\%$). Although dry mouth was significantly more in the tizanidine group (MD: 5.35; 95% CI: 1.72, 16.62; $P = 0.004$; $I^2 = 0\%$), postoperative nausea/vomiting and dizziness were comparable. Tizanidine reduces intraoperative opioid consumption without significant adverse events. However, it does not provide effective opioid-sparing analgesia or reduced opioid requirement in the first 24 hours after surgery.

Key words: Acute pain, meta-analysis, postoperative pain, systematic review, tizanidine

Introduction

The United States Food and Drug Administration (US-FDA) has licensed tizanidine, a centrally acting 2 agonist, for the treatment of multiple sclerosis, spinal cord injuries, different degenerative brain disorders, traumatic brain injury, and stroke. Tizanidine is beneficial in treating a variety of chronic pain conditions, including migraine headaches, lumbosacral

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pain, and chronic neck pain. Once ingested, the imidazoline derivative tizanidine increases the presynaptic inhibition of motor neurons while preventing the release of excitatory amino acids like glutamate and aspartate.[1,2]

When administered as a premedication, tizanidine has been shown to reduce the minimum alveolar concentration of sevoflurane for general anesthesia by 18%.[3] Tabari *et al*.[4] demonstrated that when administered as a 4 mg oral dose, tizanidine provided hemodynamic stability during induction and surgery and decreased the dose of propofol used without any significant adverse effects.

Tizanidine has been shown to have anti-nociceptive and anti-convulsant properties, which are purportedly mediated by spinal polysynaptic pathways. It has been used successfully to manage low back aches of varying etiologies successfully either alone or as a part of multimodal analgesia in several studies. The drug has shown to be well tolerated and does not pose serious side effects.[5-8] Several studies investigated preoperative tizanidine as a component of multimodal analgesia perioperatively and its efficacy as an opioid-sparing medication.[9-13] To date, there has been no systematic review that investigated the safety and efficacy of oral tizanidine in adult patients undergoing elective surgeries. Therefore, we sought to assess the role of oral tizanidine premedication in adult patients undergoing various elective surgeries.

Methods and Materials

Search strategy and criteria

We registered the protocol for this systematic review with PROSPERO which is an international prospective register of systematic reviews with the following registration number: CRD42022368546. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and the Cochrane Handbook for Systematic Reviews of Interventions were followed for conducting this systematic review.[14] We searched PubMed/Medline, the Cochrane Reviews Library (CENTRAL), Scopus, Ovid, and clinical trials.gov from the year 2000 till September 2022. The language was restricted to English. The searches were rerun before the final analysis.

The search approach made use of the following keywords: (Tizanidine) AND (acute pain OR Postoperative pain). Our study included research articles comparing tizanidine premedication with a placebo or no premedication in adult patients undergoing various elective surgeries. Studies that compared tizanidine with another premedication or had an active control group were excluded. Case reports, editorials, commentaries, reviews, publications with only abstracts, and all other types of writing were excluded.

Study selection and data extraction

Two authors independently reviewed the titles and abstracts, and they eliminated any duplication (AN and MR). After careful deliberation between the two authors, who also reviewed the entire texts, the final included studies were decided upon. An independent third author resolved any discrepancies and inconsistencies (NB). The corresponding author was contacted via email for studies where data was either not reported in the results or not present in additional files to determine appropriateness for analysis. Conference abstracts with omitted information on study design or data were not included in the analysis.

Two authors collected the relevant information, such as author information, publication dates, sample size, age, sex, and surgery details. The main result of this study was intraoperative opioid consumption. Other comparisons included 24-hour opioid consumption, postoperative pain scores at different time intervals, time to rescue analgesia, postoperative nausea and vomiting (PONV), dizziness, dry mouth, bradycardia, constipation, and urine retention side events. An independent third author resolved any discrepancies and inconsistencies (NB).

Methodological quality assessment

The methodological quality and risk of bias of the included randomized control trials were assessed using the Revised Cochrane risk-of-bias instrument for randomized trials (RoB2).[15]

To assess bias, six areas were taken into account: randomization bias, deviation from intended intervention bias, missing data bias, outcome measurement bias, selection bias for reported results, and overall bias.

Meta-analysis

A quantitative review was conducted after the qualitative review. The quantitative meta-analysis comprised all included studies that directly evaluated patient outcomes between those who received tizanidine premedication and were compared with placebo/no active premedication.

Statistical analysis

Dichotomous variables were evaluated using the Mantel–Haenszel method, and the risk ratio and its corresponding 95% confidence interval (CI) were calculated. The mean difference (MD) with the associated 95% CI for continuous variables with units-unified was calculated using the inverse variance method. The I2 statistic, which was defined

as 0–40%—might not be important, 30–60%—may represent moderate heterogeneity, 50–90%—may indicate significant heterogeneity, and 75–100%—considerable heterogeneity, was used to assess the heterogeneity between trials.[16]

The investigation made use of Review Manager 5.4.1 (Cochrane Collaboration, Software Update, Oxford, UK).[17] The results were evaluated with the random effects model and the fixed effects model, and ultimately the reliability of the combined results was examined by the degree of consistency of the results. For the meta-analysis, the fixed effects model was employed when $P > 0.01$ and I2 was less than 50% and the random effects model when $P < 0.01$ and I2 was more than 50%.

Results

Results of literature search

We searched PubMed/Medline, SCOPUS, CENTRAL, Ovid, and clinical trials.gov for randomized controlled trials (RCTs) and observational studies comparing tizanidine with control in patients undergoing elective surgeries. We identified 202 articles by searching the above-mentioned databases and registries. After removing duplicates and also articles that were not relevant, we identified 16 articles for scrutiny. A total of 13 studies were considered eligible. From these eight studies were excluded (study with no control group-1, review articles-1, active control group-3, unrelated primary and secondary outcomes-3). Finally, we included five studies which included 280 patients for analysis (140 in the tizanidine group and 140 in the control group), [Figure 1]. All the included studies are summarized in Table 1.

Risk of bias

The risk of bias within the trials according to ROB2 is depicted in Figure 2a. The summary plot of the quality assessment is shown in Figure 2b. The bias from the randomization process was low in all five studies.[9-13] Bias due to deviations from intended interventions (allocation concealment) was low in all five studies.[9-13] Bias arising due to missing outcome data was low in four studies[9-12] with no information in one study.[13] Bias in the measurement of outcome was low in four studies,[9-12] and there was no information in one study.[13] Bias arising due to the selection of reported results was low in four studies,[9,11-13] and there was no information in one study.[10] The overall bias was low in all four studies.[9-13]

Primary outcome meta-analysis

Five studies fulfilled the inclusion criteria and were subjected to qualitative analysis.[9-13] In three studies by Talakoub *et al*., Yazicioğlu *et al*., and Dadmehr *et al*., the control group was placebo or no premedication.[9,10,12] In the study by Ahiskalioglu *et al*.[11] there were three groups of 20 patients each: The first group received bilateral superficial cervical plexus block (BSCPB) with saline with oral placebo, the second group received BSCPB with 0.25% bupivacaine and oral placebo, and the third group received BSCPB with oral tizanidine premedication. The enrolled patients in group 1 (control) and in group 3 (tizanidine group) were used for the analysis. In the study by Aezi *et al*.,[13] there were three groups with 25 patients in each group. Patients in group A received 4 mg of oral tizanidine premedication, group B patients received 4 mg of oral clonidine premedication, and patients in group C received a placebo. The patients in groups A and C were used for analysis.

Meta-analysis of intraoperative opioid consumption

Two studies reported intraoperative opioid consumption (50 patients in the tizanidine group and 50 patients in the control group). The pooled analysis indicated that intraoperative opioid consumption was significantly less in the tizanidine group when compared to the control group (MD: -2.40; 95% CI: -4.22, -0.59; $P = 0.010$). A fixed effect model revealed that there was no heterogeneity among the included studies ($P = 0.40$; $I^2 = 0\%$) [Figure 3a].

Meta-analysis of 24 hours opioid consumption

24-hr opioid consumption was reported by two studies (55 patients in the tizanidine group and 55 patients in the control group). On pooled analysis, the 24-hr opioid consumption was comparable between both groups (MD: -42.53, 95% CI: -91.45, 6.39; $P = 0.09$). A random effect model was applied which was suggestive of considerable heterogeneity ($P < 0.00001$; $I^2 = 99\%$) [Figure 3b].

Meta-analysis of time to rescue analgesia

Time to rescue analgesia was reported by two studies (65 patients in the tizanidine group and 65 patients in the control group). Pooled analysis revealed that time to rescue analgesia was comparable between both the groups (MD: 308.22; 95% CI: -263.67, 880.11, $P = 0.29$). A random effect model was applied which was suggestive of considerable heterogeneity ($P < 0.00001$; $I^2 = 100\%$) [Figure 3c].

Meta-analysis of pain scores

Pain scores were reported at various intervals. However, we could perform a pooled analysis of the pain scores at 6,12, and 24 hours only because it was reported by at least two studies as an outcome.

Pain scores at 6 hours were reported by three studies (85 patients in the tizanidine group and 85 patients in the control group). A pooled analysis revealed comparable pain scores at 6 hrs between both groups (MD: -1.37; 95% CI: -3.68, 0.94; $P = 0.24$). A random effect model was suggestive of considerable

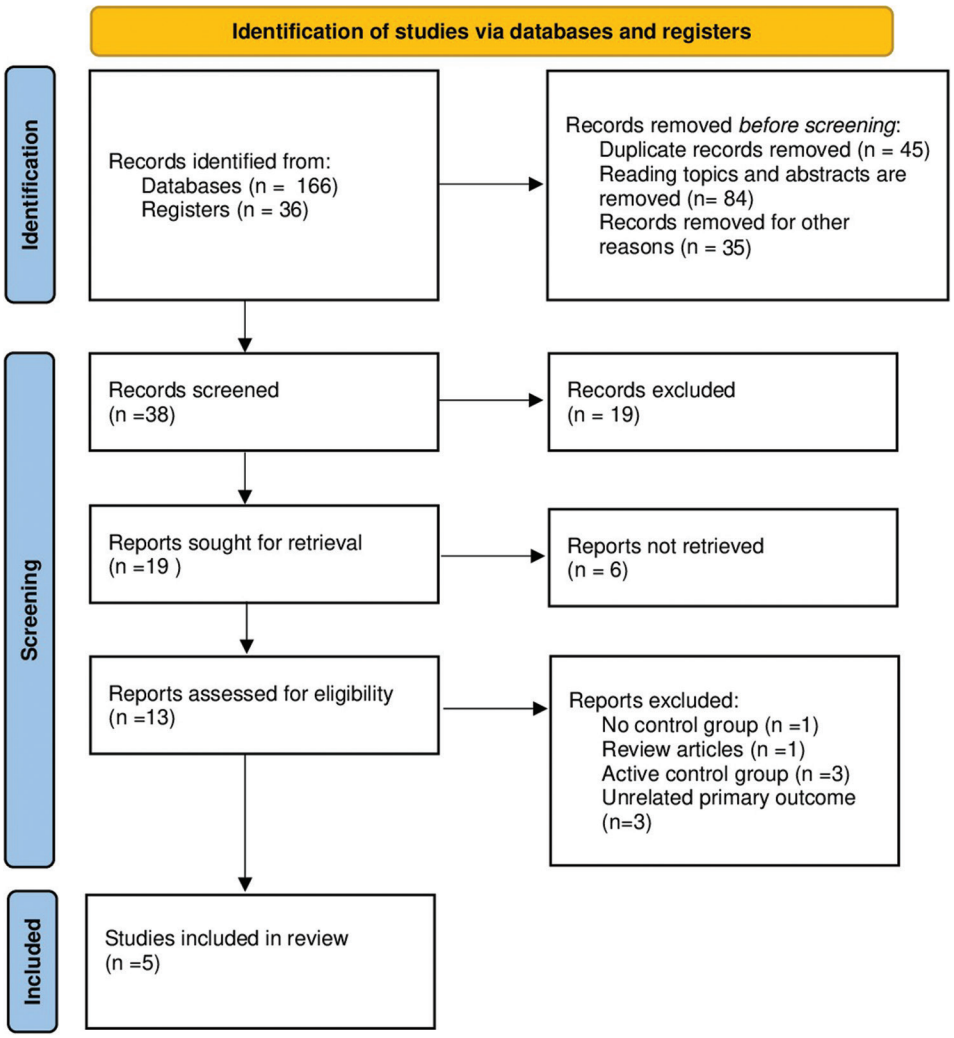

Figure 1: PRISMA flowchart

heterogeneity ($P < 0.00001$; $I^2 = 97\%$) [Figure 4a]. Pain scores at 12 hours were reported by four studies (105 patients in the tizanidine group and 105 patients in the control group). A pooled analysis revealed comparable pain scores at the end of 12 hours between both groups (MD: -1.76; 95% CI: -4.06, 0.53; $P = 0.13$). A random effect model revealed significant heterogeneity ($P < 0.00001$; $I^2 = 95\%$) [Figure 4b]. Pain scores at the end of 24 hours were reported by four studies ((105 patients in the tizanidine group and 105 patients in the control group). A pooled analysis revealed significantly improved pain scores at the end of 24 hours in the tizanidine group when compared to the control group (MD: -1.10; 95% CI: -1.50, -0.69; $P < 0.0001$). A fixed effect model was applied which did not reveal any heterogeneity ($P = 0.67$; $I^2 = 0\%$) [Figure 4c].

Meta-analysis of various adverse events

PONV as an adverse event was reported by three studies (75 patients in the tizanidine group and 75 patients in the control group). A pooled analysis revealed comparable PONV in patients of both groups (MD: 1.66; 95% CI: 0.43, 6.44; $P = 0.47$). A random effect model was applied which was suggestive of significant heterogeneity ($P = 0.12$; $I^2 = 58\%$) [Figure 5a]. Dizziness as an adverse event was reported by three studies (75 patients in the tizanidine group and 75 patients in the control group). On pooled analysis, dizziness was comparable among both groups (MD: 2.20; 95% CI: 0.84, 5.72; $P = 0.11$). A fixed effect model revealed no heterogeneity between the included studies ($P = 0.79$; $I^2 = 0\%$) [Figure 5b]. Dry mouth as an adverse event was reported by three studies (85 patients in the tizanidine group and 85 patients in the control group). On pooled analysis, the incidence of dry mouth was significantly more in the tizanidine group when compared to the control group (MD: 5.35; 95% CI: 1.72, 16.62; $P = 0.004$). A fixed effect model revealed no heterogeneity ($P = 0.94$; $I^2 = 0\%$) [Figure 5c]. Other adverse effects like bradycardia, urinary retention, and headache were reported by only one study. Therefore, a pooled analysis was not performed.

Table 1: Characteristics of included studies

Authors/ year	Country	Type of study	Number of patients	Comparator	Surgery	Primary outcome	Secondary outcome	Conclusions
Yazicioğlu *et al*/2016	Turkey	Randomized double-blind study	60	Placebo	Inguinal herniorrhaphy	Postoperative pain scores	Total analgesic consumption, return to normal life, quality of life	Tizanidine premedication decreased postoperative pain and analgesic consumption and improved return to normal activity and quality of life
Talakoub *et al*/2016	Iran	Randomized double-blind study	70	Placebo	Laparoscopic cholecystectomy	Postoperative pain scores	Time to rescue analgesia, total opioid consumption, adverse events	Tizanidine premedication before laparoscopic cholecystectomy reduced postoperative pain, opioid consumption, stay in recovery room without any complication
Ahiskalioglu *et al*/2018	Turkey	Randomized-controlled double-blind study	40	Placebo	Thyroidectomy	Pain scores	Opioid consumption, rescue analgesia, posterior neck pain, headache, and opioid-related adverse events	Pre-emptive oral tizanidine reduced postoperative opioid consumption, posterior neck pain, and occipital headache
Dadmehr *et al*/2022	Iran	Triple-blind randomized clinical trial	60	Placebo	Bimaxillary orthognathic surgery	Postoperative pain scores	Overall opioid consumption	Oral tizanidine was effective in reducing postoperative pain following bimaxillary orthognathic surgery
Aezi *et al*/2022	Iran	Double-blinded randomized study	50	Placebo	Lumbar fusion surgery	Postoperative pain scores	Opioid consumption, adverse events	Addition of oral tizanidine reduced postoperative pain when compared to a placebo

Discussion

Summary of results

This systematic review and meta-analysis investigated the efficacy and safety of oral tizanidine premedication in adult patients undergoing elective surgeries. The pooled analysis revealed that oral tizanidine premedication reduced intraoperative opioid consumption and provided significantly lower pain scores at 24 hrs after surgery when compared to control but with comparable pain scores at 6 and 12 hours. The incidence of dry mouth was significantly more with tizanidine premedication when compared to the control group. However, other adverse events like PONV and dizziness were comparable in both groups. To the best of our knowledge, this is the first systematic review that has investigated the safety and efficacy of oral tizanidine premedication in adult patients when compared to no premedication or placebo for elective noncardiac surgeries.

Several studies investigated tizanidine in alleviating induced thermal hyperalgesia in the Sprague Dawley rat model after surgery. The authors concluded that tizanidine could reverse thermal hyperalgesia in these rat models.[18] Omote *et al*.[19] compared oral premedication with clonidine (150 μg), triazolam (0.25 mg), and tizanidine (3 mg) in 63 patients undergoing gynecological surgeries under tetracaine spinal anesthesia. The authors concluded that oral premedication with clonidine and tizanidine prolonged tetracaine spinal anesthesia. However, patients in the clonidine group developed hypotension and bradycardia. The sedative and sympatholytic effects of oral tizanidine were investigated by Miettinen *et al*.[20] in six healthy male volunteers. They used three different doses of tizanidine, namely 4,8,12 mg and compared with 150 μg oral clonidine. Their analysis revealed that although the sedative and sympatholytic effects of both drugs were comparable, the effects were long-lasting with clonidine. This is undesirable, especially in short-duration surgeries. They also concluded that a 12 mg dose of tizanidine was equal to 150 μg clonidine but with a shorter duration of action. Subsequently, several studies were published that investigated the efficacy of tizanidine as a premedication for adult patients undergoing various surgeries.

Seventy patients undergoing laparoscopic cholecystectomy under general anesthesia were divided randomly into two groups by Talakoub *et al*.[9] Patients in one group were given 4 mg of tizanidine 90 minutes before surgery, whereas those in the other group were given a placebo. The authors concluded that pre-emptive tizanidine reduced pain scores, decreased opioid usage, and decreased recovery room stays. Yazicioğlu *et al*.[10] randomly assigned 60 patients having standard general anesthesia and a postoperative multimodal analgesia procedure for inguinal hernia repair. Patients were given a placebo in one group and 4 mg of oral tizanidine in

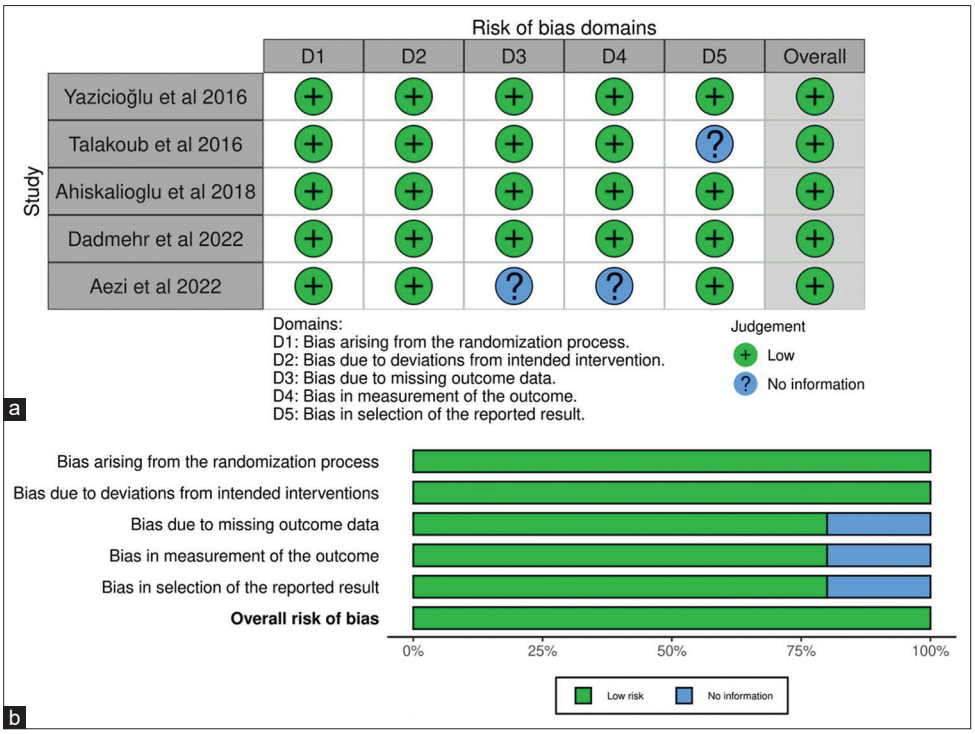

Figure 2: (a) Traffic light plot. (b) Summary plot

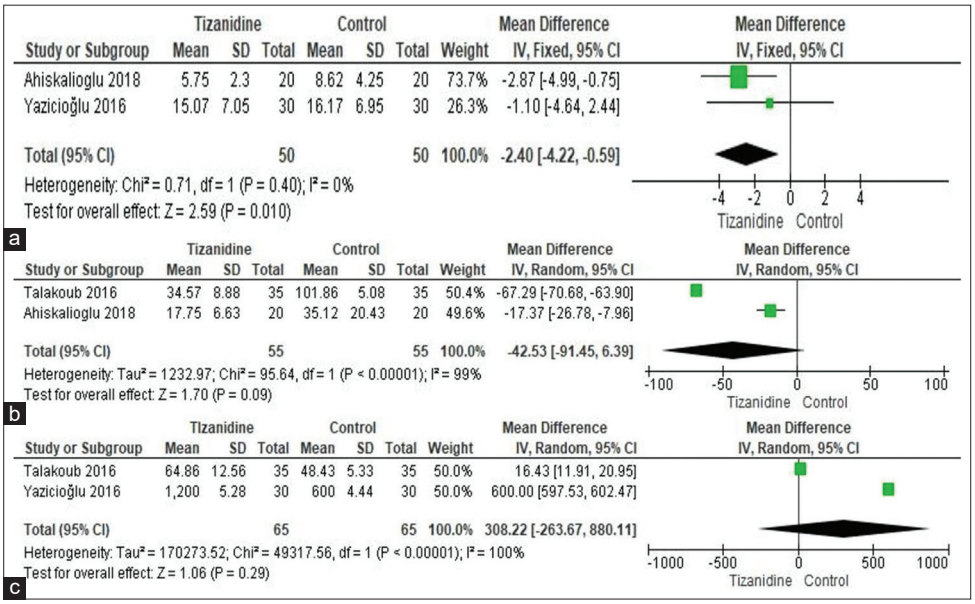

Figure 3: (a) Forest plot showing comparison of intraoperative opioid consumption. (b) Forest plot showing comparison of 24-hour opioid consumption. (c) Forest plot showing comparison of time to rescue analgesia

the other group. Based on their data, the authors concluded that patients who got preventive tizanidine had better pain scores while at rest and when moving around, used fewer opioids, and recovered more effectively. Ahiskalioglu *et al*.[11] randomly divided 60 patients undergoing thyroidectomy into three groups. Twenty patients each were given a bilateral superficial cervical plexus block (BSCPB) with a placebo in the first group, 0.25% bupivacaine in the second group, and 6 mg of tizanidine capsule as a premedication in the third group. The group that got BSCPB with tizanidine exhibited lower opioid use, postoperative pain, and occipital headache than the other groups, according to the results. Dadmehr *et al*.[12] compared the effects of 4 mg of oral tizanidine premedication in patients undergoing bimaxillary orthognathic surgery placebo (30 patients in each group). After analysis, the authors concluded that pre-emptive

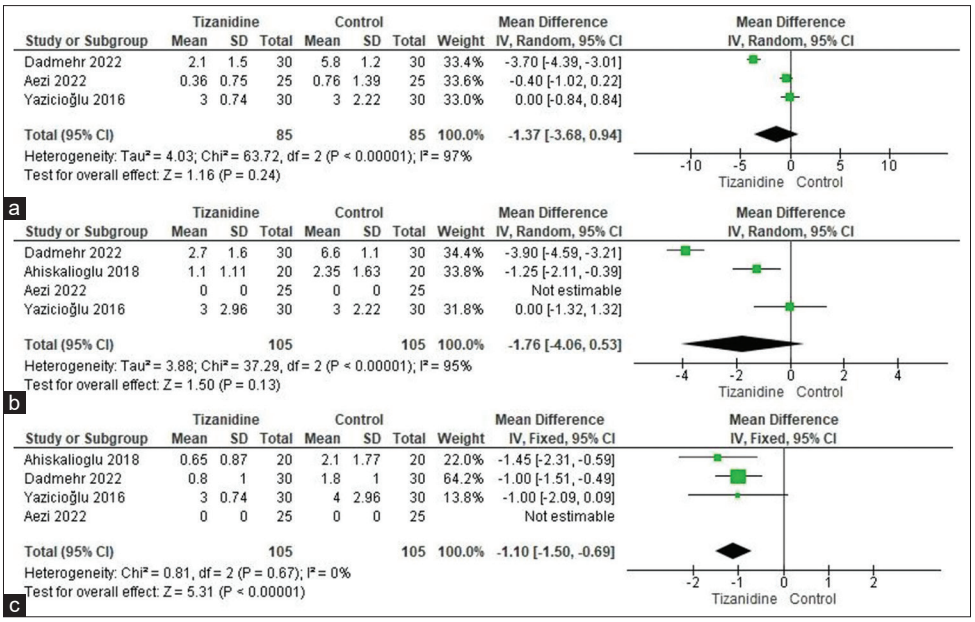

Figure 4: (a) Forest plot showing comparison of pain scores at 6 hours. (b) Forest plot showing comparison of pain scores at 12 hours. (c) Pain scores at 24 hours

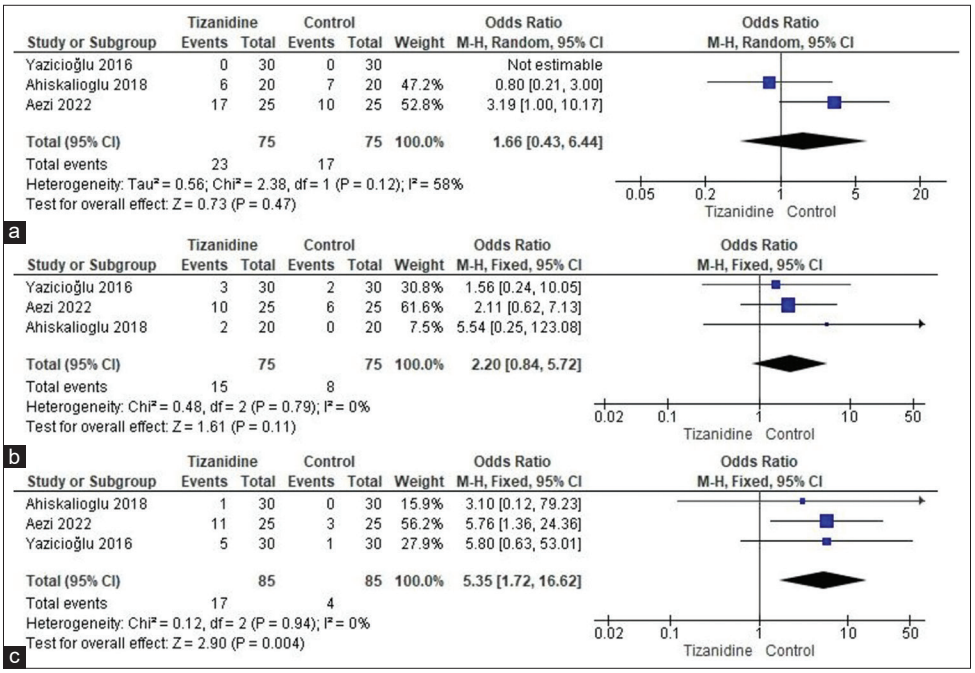

Figure 5: (a) Forest plot showing comparison of postoperative nausea/vomiting. (b) Forest plot showing comparison of dizziness. (c) Forest plot showing comparison of dry mouth

tizanidine, when compared to a placebo, not only reduced postoperative opioid intake but also improved postoperative pain levels. Aezi *et al*.[13] randomized 75 patients undergoing lumbar fusion surgery into three groups: One group received 4 mg tizanidine, the second group received 4 mg clonidine, and the third group received a placebo. On analysis, the authors concluded that patients who received tizanidine and clonidine had comparable pain scores and comparable adverse events.

The pooled analysis revealed that intraoperative opioid consumption was significantly less with tizanidine premedication when compared to placebo or control. Pain scores at 6 and 12 hours postoperatively were comparable. Moreover, 24-hr opioid consumption and time to rescue analgesia were also comparable. This could be because of the relatively short duration of the action of tizanidine. This also suggests that tizanidine premedication could prove effective in indicated patients undergoing short-duration

surgeries (less than 90 minutes). In cases of renal and hepatic impairment, tizanidine should be taken cautiously.[21-23] In patients taking clonidine and getting dexmedetomidine during surgery, it should be avoided due to the similar pharmacological profile. Patients on beta-blockers, with pre-existing low heart rates, and labile blood pressures need to be monitored after the premedication because tizanidine is known to produce hypotension and bradycardia.[1,24,25]

The strength of this study is that this is the first systematic review that investigates the efficacy and safety of oral tizanidine premedication in adult patients undergoing elective surgeries. Although only five studies fulfilled the inclusion criteria with an overall small sample size, the risk of bias among the included studies was considerably low. There were several limitations of this review. Since the number of included studies was less, the sample size for pooled analysis was less. Many essential outcomes like pain scores, hemodynamics, and opioid requirements were inconsistently reported. All patients in the tizanidine group in included studies received 4 mg oral premedication except in the study by Ahiskalioglu *et al*.[11] where the dose administered was in the form of a 6 mg capsule. The patient satisfaction scores and quality of recovery scoring were also not reported consistently. The quantitative examination of several variables revealed heterogeneity, which could be attributed to different study designs, varying sample sizes, and inconsistent data reporting. Further studies with adequate sample size and appropriate study design to address various biases like attrition, blinding, and reporting need to be conducted before establishing tizanidine as a part of the multimodal analgesia armamentarium for the perioperative period.

Conclusion

Based on the results of this systematic review and meta-analysis, oral tizanidine premedication could reduce intraoperative opioid consumption with tolerable adverse events. However, the medication does not translate into better pain scores when compared to a placebo. This could be due to heterogeneity in the surgeries, heterogeneity in the study outcomes, small sample size, and inconsistent outcomes reported. The most effective and tolerable dose of tizanidine as well as various surgeries where tizanidine can be utilized successfully need to be explored by well-designed, adequately powered studies.

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Conflicts of interest
There are no conflicts of interest.

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