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Research Article

Effectiveness and Safety of Clonidine for Controlling Blood Loss, Hemodynamic Stability, and Surgical Field Quality in Oral and Maxillofacial Surgery: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background: Clonidine is an α-adrenoreceptor agonist that reduces sympathetic outflow and releases certain neurotransmitters by acting on receptors in the brain and peripheral tissues. The aim of this systematic review and meta-analysis is about the effectiveness and safety of clonidine for controlling blood loss, hemodynamic stability and surgical field quality comparing with tranxemic acid, placebo and dexmedetomidine. The randomized controlled trials that determine the effect of clonidine on blood loss, hemodynamic stability, and surgical field quality in adult patients undergoing oral and maxillofacial surgery were included. The articles included in this systematic review were searched through the electronic databases PubMed, Cochrane Library, and Google Scholar from July to September 17, 2025. The primary outcomes were controlling blood loss, hemodynamic stability, and surgical field quality. Secondary outcomes were duration of surgery and adverse events. The risk of bias was assessed by the Cochrane Collaboration tool (ROB2). Subgroup and sensitivity analysis was conducted to investigate the study of high risk of bias. Mean difference and relative risk with a 95% confidence interval were used for analysis. There were 15 articles included in the review after screening 615, with a total population of 1143. Clonidine was less blood loss than tranxemic acid (MD=40.17, 95% CI: 4.95- 75.38; p=0.03), more blood loss control than with placebo (MD=-75.15, 95% CI: -96.04-54.25; p <0.00001), and less blood loss control than with dexmedetomidine (MD=7.65, 95% CI: 1.19-14.11; p=0.02). Clonidine maintained mean arterial blood pressure than placebo (MD = -3.87, 95% CI: -6.01--1.72; p = 0.0004). Clonidine is maintained MAP in normal range than placebo when administered Pre-induction (MD=-1.88,95% CI: -3.7--0.07; p=0.04) compared with post induction (MD = -8.16.95% CI: -13.7--2.62; p=0.004). Clonidine has less poor and fair surgical field quality than placebo (RR=0.1, 95% CI: 0.02-0.42, p=0.002; RR=0.82, 95% CI: 0.67-1, p=0.05) respectively. Clonidine decreases blood loss more than placebo. Clonidine is less likely inferior to dexmedetomidine to reducing blood loss for oral and maxillofacial surgery. Clonidine maintains mean arterial blood pressure in the normal range than placebo when administered pre-induction than after induction. Clonidine maintains MAP before induction, and it is effective pre-induction as well as post-induction to maintain a mean heart rate comparable with dexmedetomidine. Clonidine is shortening the duration of surgery comparably with tranxemic acid and dexmedetomidine but more than placebo.

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Keywords

Blood Loss, Clonidine, Effectiveness, Hemodynamic, Surgical Field Quality

1. Introduction

Maxillofacial procedures lead to excessive blood loss, up to 11%, during fracture due to the rich vasculature in oral and face surgery. In addition to that surgical intervention, the time of surgery, anesthesia technique, and methods of hemostasis may enhance surgical blood loss. Controlling blood loss improves the hemodynamics of patients, reduces the blood transfusion requirement and its complications, and improves temperature regulation and coagulation disorders [1] Furthermore, it creates a blood-free surgical area, better visibility, and shorter operation time [2].

Surgical, Anaesthetic and haemostatic are strategies used for controlling blood loss. Permissive hypotension, neuraxial anesthesia, and adequate ventilation are anaesthetic methods for reducing bleeding. Purposefully reducing blood pressure creates a desirable clean surgical area [3]. Anaesthesiologists have recommended a variety of medications to induce hypotension, such as remifentanil, propanol, and volatiles. To enhance the hypotensive effect of first-line medications, peripherally acting vasodilators such as labetalol and nitroglycerine have been employed [4].

Besides to peripherally vasodilators, central acting adrenoreceptor agonists are used for permissive hypotension and controlled blood loss today. From those medication, clonidine is an α-adrenoreceptor agonist that reduces sympathetic outflow and releases certain neurotransmitters by acting on receptors in the brain and peripheral tissues. It is used in therapeutic settings for more than 50 years, mostly as an antihypertensive agent [5].

Despite its extensive history, clonidine was first used epidurally in human anesthesia in 1984. Among its significant pharmacological properties for anesthesia practice are hypnosis, analgesia, a decrease in the demand for opioids, and an anti-sympathetic reaction to surgical trauma [6].

2. Objective

The aim of this systematic review and meta-analysis is to explore the effectiveness and safety of clonidine for controlling blood loss, hemodynamic stability, and surgical field quality among adult patients undergoing oral and maxillofacial surgery. The primary reason for comparing tranxemic acid and clonidine is that the former is an antifibrolytic that increases the risk of thrombosis and other complications, as well as its costs; therefore, it is crucial to reduce these risks [7-9].

3. Methods and Materials

3.1. Study Selection and Eligibility Criteria

The appraised references were depending on inclusion and exclusion criteria. The included studies were-

All randomized controlled trials involving adult patients undergoing oral and maxillofacial surgery undergoing general anesthesia, randomized controlled trials with full text mentioned the clonidine uses in intraoperative bleeding, hemodynamic stability, and surgical field quality, Control group with tranxemic acid, placebo and dexmedetomidine.

Exclusion criteria

An article that is not related to the clonidine effect on intraoperative bleeding, which has no full text, and lack of authorship, study design (Cohort, case control cross-sectional study, and retrospective study), animal study.

The review was registered to PROSPER https://www.crd.york.ac.uk/PROSPERO/ID177825.

3.2. Searching Strategies

The electronic databases such as PubMed, Cochrane Library, and Google Scholar were used for searching for this systematic review between July and September 17, 2025. For the Cochrane Library, we utilized the medical subject heading (MESH) word. The Boolean operators "AND" and "OR" were utilized and outcome findings were composed using the medical subject heading (MeSH). For an example using a Cochrane Library search method. Alpha 2 agonist (Mesh) term "AND" blood loss, alpha 2 agonist (MeSH) "AND" maxillofacial, alpha 2 agonist (MESH) "AND" blood loss, and alpha 2 agonist (MeSH) "AND" controlling… *After searching up to saturation, we took only randomized controlled trials and matched them to our study. Language was restricted to English. In the references papers list, all articles included in the trials and systematic review matched our inclusion criteria.* Mendeley reference 2.138.0 was used to download all of the papers and eliminate duplicates.

3.3. Data Collection and Analysis

3.3.1. Selection of Studies

Four authors were involved in the collection of data independently before it was inserted into Excel. The first two authors, T. A. and D. T., were initially excluding duplication by using Mendeley reference, and the next authors, S. M. and E.

A., were evaluating whether the collected articles met the finding topic depending on the title and abstract. Each of the reviewers independently retrieved and checked the screened data to fulfil eligibility criteria depending on the author's name, year of publication, sample size, type of procedure, blood loss, hemodynamic stability, grading of surgical field quality, and duration of surgery. Disagreements were resolved by T. T. and K. M.

3.3.2. Data Extraction

Data was collected on the review of articles depending on the characteristics of the study (author, study design, sample size, country of study, and year of study), intervention (dose of medication, duration of medication given, placebo versus medication or medication versus placebo), and comparator and outcome (bleeding, hemodynamic stability, surgical field visualization, and duration of surgery). In the study the collected articles were all randomized controlled trials. An Excel spreadsheet and Review Manager (version 5.4.1) were used for data extraction (Table 2). During data collection for blood loss, which is measured in haematocrit and haemoglobin, we converted it to total blood volume using estimated blood volume*(haematocrit initial-haematocrit final)/haematocrit initial. The raw data, which are measured in a single time interval, were changed into mean and standard deviation. Combined mean with a formula of x1*n1+x2*n2/n1+n2 when x1 is the mean in one group and x2 is the mean in the second group and n1 and n2 are sample 1 and sample.

3.4. Data Analysis

Review Manager version 5.4.1 software was used for data analysis. Mean difference (MD) with 95% CI for continuous data and relative risk (RR) with 95% confidence interval for dichotomous data. Heterogeneity was assessed with I^2 and Chi^2. A p-value < 0.05 is considered as heterogeneity from chi-square. Egger's test was used to check publication bias after funnel plot asymmetry was checked. Egger's test was done using STATA version 14, and a value of (P<0.05) was considered as publication bias. We used a forest plot for pairwise and subgroup analysis. We used the random effect model for heterogeneity $I^2 \geq 50$ and greater than three studies and Fixed effect model for heterogeneity $I^2 \leq 30$. We performed the following subgroup analysis to explore sources of heterogeneity: for hemodynamic parameters (mean of arterial pressure and heart rate), subgroup analysis by measurement timing (pre-anesthetic induction versus post-induction). For surgical field quality, we reported risk ratio stratification by Boezaart scale: good (0-1), fair (2-3), and poor (4-5). subgroup analysis for hemodynamic stability and surgical field quality. Post-hoc subgroup analysis was also conducted among study placebo vs clonidine, clonidine vs dexmedetomidine for hemodynamic stability before.

4. Results

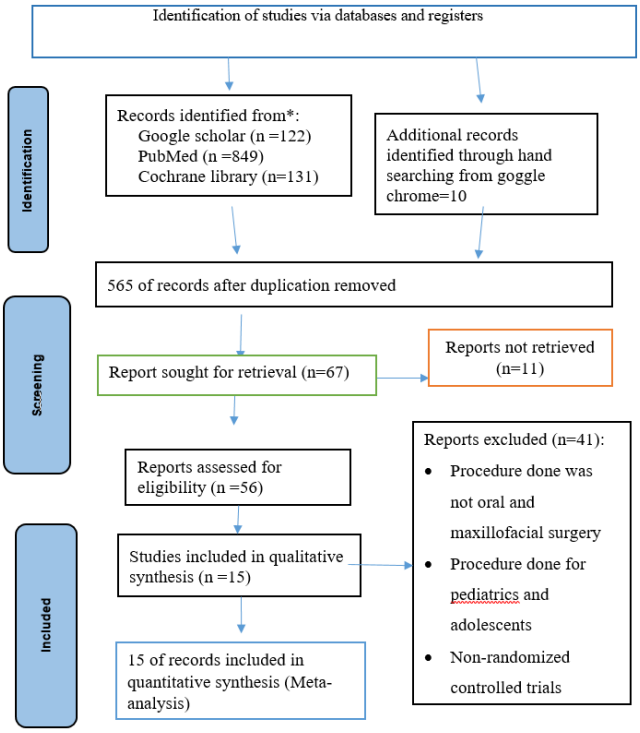

Figure 1. *PRISMA Flow chart shows clonidine for controlling of blood loss, hemodynamic stability and surgical field quality among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

849 articles from PubMed through MEDLINE, 122 from Google Scholar, 131 articles from the Cochrane Library, and 10 from grey literature were searched. After duplication was removed by Mendeley reference, 615 articles were screened. Finally, 15 randomized controlled trials that contain clonidine compared with tranxemic acid, placebo, and dexmedetomidine were included in the study (Figure 1).

From 15 articles fit for final analysis, three articles contain a sample size of 264 (23.2%) comparing tranxemic with clonidine [7-9], six articles compare clonidine with placebo have 443 (38.9%) sample size [10-15] and five articles compare clonidine with dexmedetomidine have 436 (38.3%) [16-20]. The range of sample size was from 40-120.

4.1. Study Characteristics

The characteristics of included studies were summarized in (Table 1). From the gathered studies, 13 were published in Asian countries (9 articles in India and 4 in Iran) and 2 in Africa (Egypt). The mean age of participants was 38.1. Female patients account for about 34.6%, and males account for 65.4% in the comparison of tranxemic acid with clonidine from a total sample size of 264. The ratio of male to female in the comparison of clonidine with placebo is 1.39. Greater than half

(51.5%) of dexmedetomidine group is male while the remaining is female, similarly 55.6% male and 44.4% is clonidine group during comparison.

Table 1. *Excel spread sheet for clonidine for controlling of blood loss, hemodynamic stability and surgical field quality among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

Author	Year	Area	study design	S. size	Intervention	Main outcome
Jan et. al	2014	India	RCT	120	Oral clonidine 5 mcg/kg vs famotidine 40mg	oral clonidine reduce bleeding in endoscopic sinus surgery
Khandelwal et al	2023	India	RCT	60	Clonidine 200 mcg 60 minute before surgery vs sip water before 60 minutes	Pre-emptive clonidine reduces surgical bleeding by controlling haemodynamic in FSS
Arafat et al	2024	Egypt	RCT	40	2 mcg oral clonidine taken 1 to 1.5 hours before operation	Premedication of oral clonidine improves hemodynamic status, surgical field, decrease blood loss
M. B. Heydari, M. Safdari, B. Hmmatopoor	2024	Iran	RCT	92	TXA 700mg/kg 2 hours before surgery and Oral clonidine 2mcg/kg 90 minute before surgery	Use of TXA compared with clonidine more control of bleeding in Rhinoplasty
Von et al	2024	Egypt	RCT	80	3mcg/kg clonidine diluted in 10 ml 0.9% NS followed by infusion 0.4mcg/kg /hr vs 1mcg/kg Dex diluted in 10ml of 0.9%NS followed by infusion of 0.4mcg/kg/hr	both dexmedetomidine and clonidine good to excellent surgical field visuality, blood loss and duration of surgery are comparable
suggala kk. et al	2020	India	RCT	60	3mcg/kg of clonidine in diluted of 10ml of 0.9%NS infused over 10 minutes before induction followed by infusion vs 1mcg/kg of Dex. diluted in 10 ml 0.9% NS 10 minute before induction followed by infusion 0.4-0.8 mcg	Clonidine is used as hemodynamic stability, safe operative field Visuality, decreased blood loss
Krishna et al	2025	India	RCT	80	3mcg/kg of clonidine diluted of 100ml of 0.9%NS given 15 minute before induction vs 1mcg/kg of Dex. Diluted in 100ml of 0.9% NS given 15 minutes before induction	controlled hypotension were achieved with either Dex. or clonidine, Dex. has better haemodynamic stability, decreased blood loss, and excellent surgical field visuality than Clonidine
D, V. Praven. et al	2024	India	RCT	80	1mcg/kg of Dex. given over period of 10 minute before induction followed by infusion of 0.2-0.7 mcg/kg/hr vs 2mcg/kg of clonidine given 10 minutes of 1-2 mcg/kg/hr	Controlled hypotension, intraoperative blood loss, better surgical field vision, and postoperative recovery
Bafna et al	2021	India	RCT	70	1mcg/kg of Dex. Diluted in 10ml given over period of 10 minute before induction and followed by infusion 1mcg/kg/hr vs 2mcg/kg of clonidine diluted induction followed by infusion of 1mcg/kg/hr	both dexmedetomidine and clonidine for controlled hypo tension to improve surgical field quality. Dex. provide more hemodynamic stability and postoperative analgesia than Clonidine
Das et al	2016	India	RCT	66	IV Dex 1mcg/kg diluted in Saline given 15 minutes before induction vs IV clonidine 1.5 mcg/kg diluted	Dexmedetomidine is more effective than clonidine in controlled hypotension, less blood

Author	Year	Area	study design	S. size	Intervention	Main outcome
					in 100ml saline given 15 minutes before induction	loss, more surgical field quality and analgesia
Ghorbani J et al	2018	Iran	RCT	52	IV TXA 15nl/kg diluted in 100ml NS was given and followed by infusion 10 minute after induction vs 0.2 mg oral clonidine was given 1 to 1.5 hours before surgery by infusion	bleeding control, surgical field visualization and surgical satisfaction
Akram Hammatpoor et al	2023	Iran	RCT	120	3mcg/kg of clonidine given oraly 90 minute before surgery vs 250 mcg/kg TXA orally before 2 hours	Clonidine more effective of bleeding than TXA
Jabalameli et al	2005	Iran	RCT	113	5 mcg/kg of clonidine received 90 minutes before operation	Premedication with oral clonidine reducing bleeding and controlled hypotension with fentanyl and hydralazine for controlled hypotension
Suman Kaushik et al	2019	India	RCT	50	20 ml of normal saline in premedication vs 3mcg/kg body weight in 20 ml normal saline	clonidine is cheap and safe drug for controlled hypotension
Jiwanmall et al	2017	India	RCT	60	3mcg/kg of clonidine vs sterile water was given 30 minutes before induction	clonidine is reduce intraoperative blood loss, additional hypotensive drugs, improve surgical field quality and good analgesia

Note: RCT-randomized controlled trials, dex-dexmedetomidine

4.2. Risk of Bias Assessment

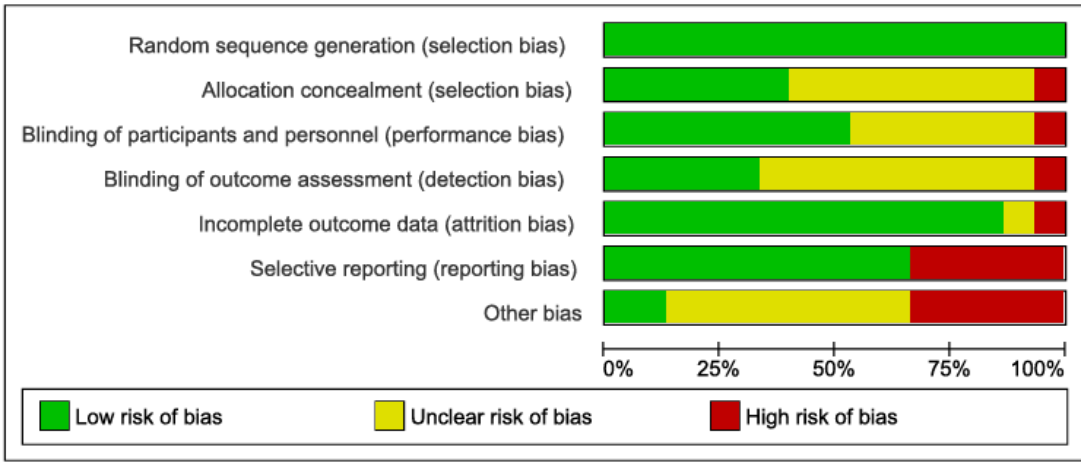

Figure 2. *Risk of bias graph of Clonidine for controlling of blood loss, hemodynamic stability and Surgical field quality among adult patient undergoing oral and maxillofacial surgery, SRMA, 2025.*

We assessed risk of bias by using Review Manager software version 5.4.1 based on the Cochrane risk of bias using ROB-2 tool [21] for randomized controlled trials. The bias assessed was based on randomization, allocation concealment, blindness of study participants, deviation due to treatment of group, measurement, follow-up, and selection of reporting outcome. The bias was assessed by two authors (T. A. and S. M.), and it was reported in the form of a risk of bias graph and a graph summary (Figures 2 and 3).

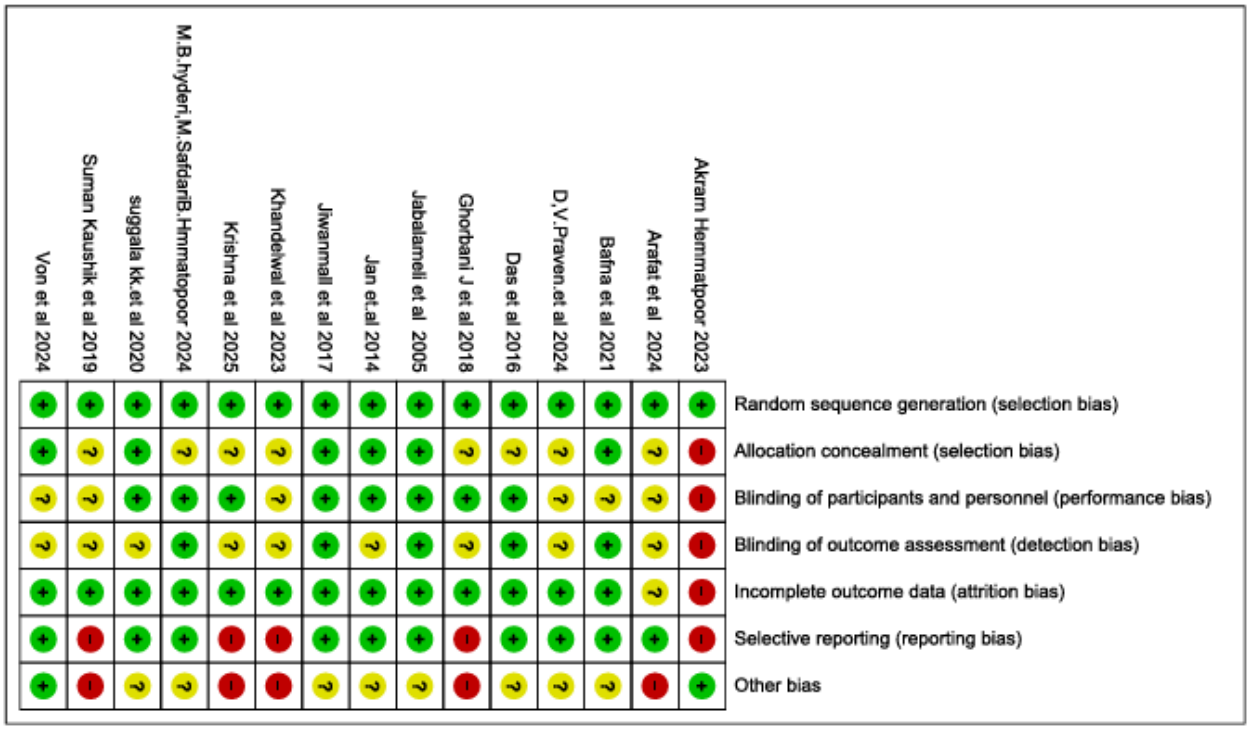

Figure 3. *Risk of bias summary of clonidine for controlling of blood loss, hemodynamic stability and surgical field quality among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

4.3. Quality of Assessment

The study included a quality assessment by using Cochrane Collaboration tools for assessing risk of bias. Over all five trials have high risk of bias. One articles have not explained adequate allocation concealment, blinding of participants, incomplete outcome data, and reporting [9]. The remaining four articles are due to lack of inadequate reporting data [12, 13, 15, 22]. One trial has some concern of risk of bias due to lack of concealment, blinding of participants or assessors, and incomplete data [20].

Quality of evidence was assessed using the GRADE approach [23] (Table S4). The evidence was graded as high, moderate, and low after assessing the risk of bias, inconsistency, indirectness, imprecision, and publication bias (Table 2).

Table 2. *Quality assessment of clonidine for controlling of blood loss, hemodynamic stability and surgical field quality among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

Author	Study design	Risk of bias	Inconsistency	Indirectness	Impression	Publication bias	Level of quality
Jan et. al 2014	RCT	Not serious	Not serious	Not serious	Not serious	Undetected	High
Khandelwal et al 2023	RCT	Not serious	Not serious	Serious	Not serious	Suspected	Moderate
Arafat et al 2024	RCT	Not serious	Not serious	Not serious	Not serious	Undetected	High
M. B. Heydari, M. Safdari 2024	RCT	Not serious	Serious	Not serious	Not serious	Undetected	Low
Von et al 2024	RCT	Not serious	Not serious	Not serious	Not serious	Suspected	Moderate
suggala kk. et al 2020	RCT	Not serious	Not serious	Serious	Not serious	Not suspected	Moderate
Krishna et al 2025	RCT	Not serious	Not serious	Serious	Not serious	Suspected	Moderate
D, V. Praven. et al 2024	RCT	Not serious	Not serious	Serious	Not serious	Undetected	Moderate
Bafna et al 2021	RCT	Not serious	Not serious	Serious	Not serious	Undetected	Moderate

Author	Study design	Risk of bias	Inconsistency	Indirectness	Impression	Publication bias	Level of quality
Das et al 2016	RCT	Not serious	Not serious	Serious	Not serious	Suspected	Moderate
Ghorbani J et al 2018	RCT	Not serious	Not serious	Not serious	Not serious	Undetected	High
Akram Hemmatpoor 2023	RCT	Serious	Serious	Not serious	Not serious	Suspected	Low
Jabalameli et al 2005	RCT	Not serious	Not serious	Not serious	Not serious	Not suspected	High
Suman Kaushik et al 2019	RCT	Not serious	Not serious	Not serious	Not serious	Not suspected	High
Jiwanmall et al 2017	RCT	Not serious	Not serious	Not serious	Not serious	Undetected	High

The grade assessment revealed that seven outcomes were graded as high quality, six outcomes were moderate due to concern of publication bias, indirectness, and inconsistency, and two were low quality due to concern of high risk of bias, publication bias, and inconsistency. The overall quality was low to moderate which downgraded the imprecision.

4.4. Ethical Statement

The study was conducted according to declaration of Helsinki and its amendment's. All study information was gathered from public data base, no ethical approval was taken for this review.

4.5. Synthesis of Results

4.5.1. Clonidine Versus Tranxemic Acid for Controlling of Blood Loss

Three studies [7-9] Compare the blood loss control of clonidine versus tranxemic acid. The study revealed that clonidine causes less blood loss than tranxemic acid (MD = 40.17, 95% CI: 4.95-75.38; p = 0.03). There is high heterogeneity among the study P<0.00001, I²=99% (Figure 4).

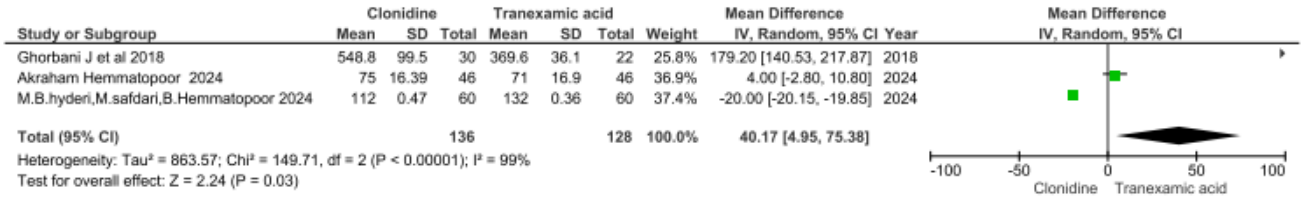

Figure 4. *Forest plot shows of comparing clonidine versus tranxemic acid on blood loss controlling among adult patients undergoing oral and maxillofacial surgery, SRMAM, 2025.*

4.5.2. Clonidine Versus Placebo for Controlling of Blood Loss

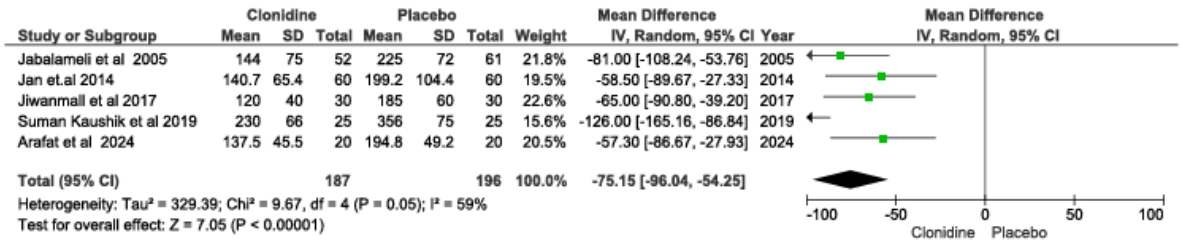

Figure 5. *Forest plot shows comparing of clonidine versus placebo on controlling of blood loss among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

There are five [10-13, 24] studies comparing the effect of blood loss control of clonidine versus placebo. This study showed that clonidine decreased blood loss more than placebo (MD=-75.15, 95% CI: -96.04 to -54.25; P <0.00001 (Figure 5). There is moderate heterogeneity (I^2 = 59%, p < 0.05) among the study group. There is no suspicion of publication bias among studies for which the Egger's test shows a p-value greater than 0.05.

4.5.3. Clonidine Versus Dexmedetomidine for Controlling of Blood Loss

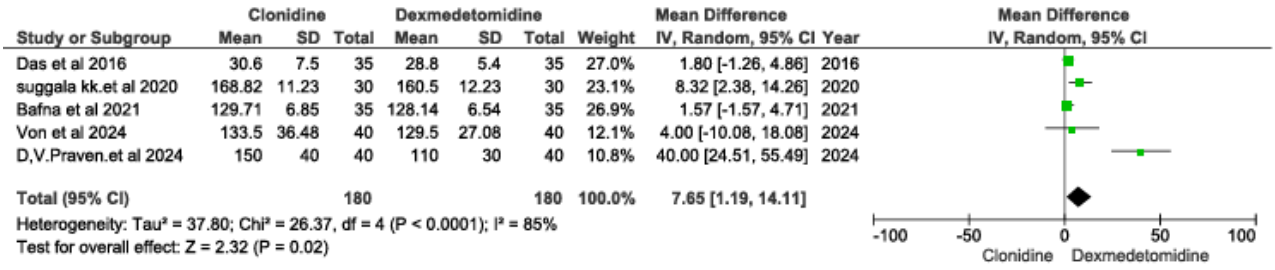

Figure 6. *Forest plot shows comparison of clonidine 3.5.2 versus dexmedetomidine on blood loss among adult patients undergoing oral and maxillo-facial surgery, SRMA, 2025.*

Five studies [16-18, 20] were included to compare the blood loss controlling between clonidine and dexmedetomidine. There is statistically significant difference among studies regarding blood loss control (MD = 7.65, 95% CI (1.19-14.11) with P = 0.02). There is statistically considerable heterogeneity, I^2 = 85%, P < 0.0001 (Figure 6). The publication bias among studies was suspected, so there is a moderate level of evidence quality.

4.5.4. Hemodynamic Stability Among Clonidine and Placebo

Comparison of mean arterial blood pressure (MAP)

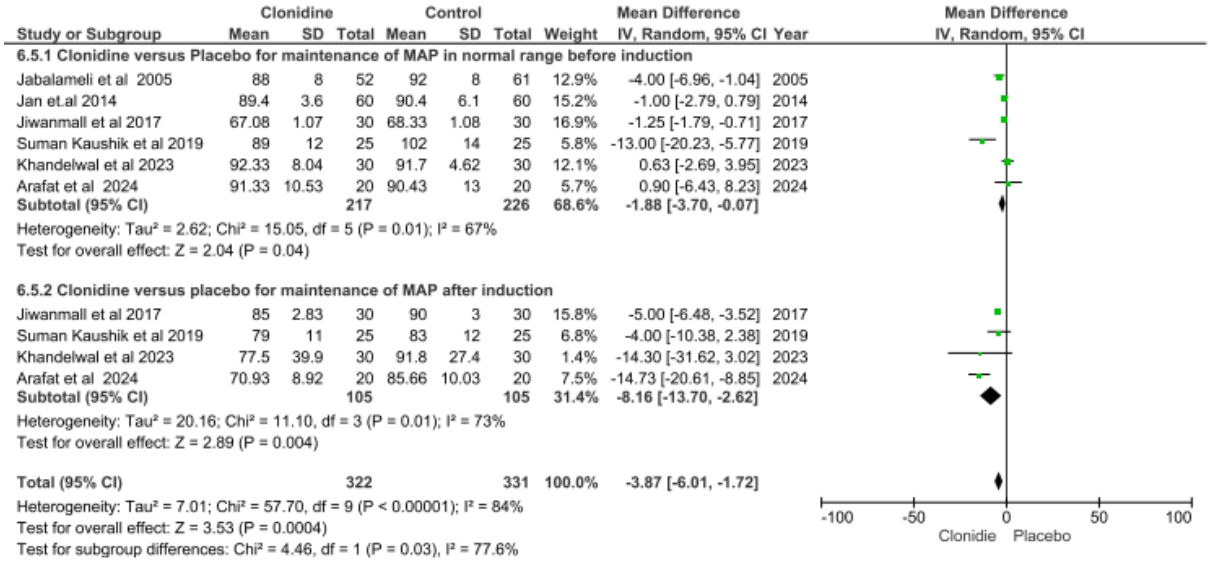

Figure 7. *Forest plot shows comparison of clonidine versus placebo on maintenance of Mean arterial pressure among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

Six studies [4, 10-13, 15, 24] revealed that pre-induction of mean arterial blood pressure is better maintained with clonidine than with placebo (MD=-1.88, 95% CI: -3.7- -0.07; p=0.04). There is moderate heterogeneity, I^2 = 67%, P = 0.01 (Figure 7). After induction of anesthesia, patients treated with clonidine also maintained a mean arterial blood pressure more than placebo (MD=-8.16, 95% CI: -13.7- -2.62; p=0.004). Heterogeneity is moderate with I^2 = 73% and P = 0.01 for these

studies (Figure 7).

4.5.5. Clonidine Versus Placebo for Maintenance of Heart Rate

Clonidine nearly maintained heart rate in a normal range comparable to placebo (MD = 0.03, 95% CI: -1.98 -2.04, P = 0.98) before induction of anesthesia. The heterogeneity among studies is moderate (I^2 = 44%), but there is no statistically significant effect of heterogeneity (P = 0.12). There are only three studies that showed the comparison of clonidine with placebo-maintained heart rate in the normal range after induction of anesthesia. So, according to this analysis, clonidine is comparable to placebo to maintain heart rate (MD=-6.36, 95% CI: -14.39 -1.68; p=0.12) (Figure 8) after induction.

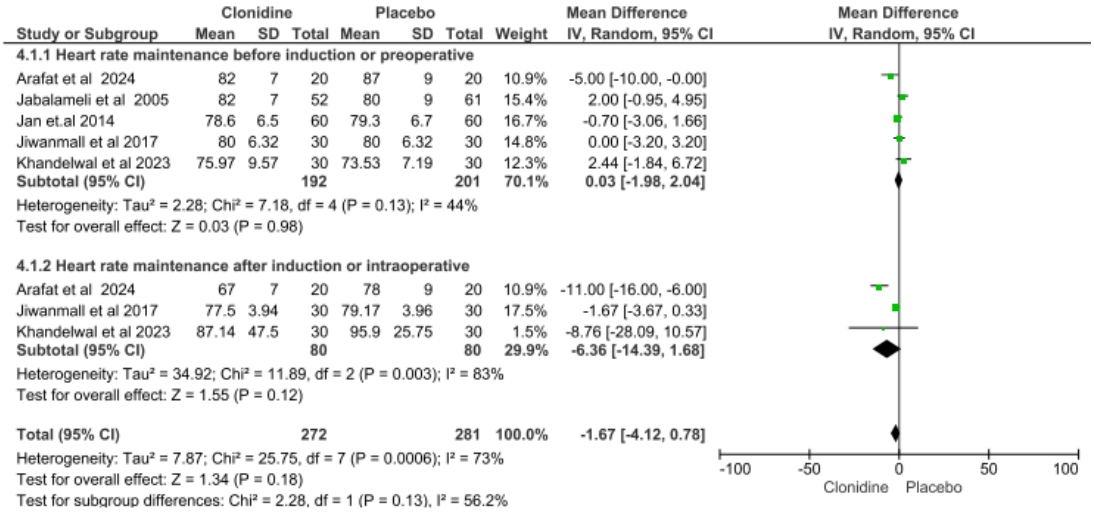

Figure 8. *Forest plot shows comparison of clonidine versus placebo on maintenance of mean heart rate among adult patients undergoing oral and maxilla 3 facial surgery, SRMA, 2025.*

4.5.6. Comparison of Mean Arterial Blood Pressure for Clonidine Versus Dexmedetomidine

Clonidine maintains mean arterial blood pressure comparable to dexmedetomidine (MD=0.09, 95% CI: -0.36 - 0.54; p=0.7) before induction, but patients who have taken clonidine maintain mean arterial blood pressure less than dexmedetomidine after induction of anesthesia (MD=3.2, 95% CI: 0.84 - 5.57; p=0.008). There is no heterogeneity (I^2 = 0%) before induction of anesthesia. These studies revealed that heterogeneity among studies is moderate with statistical non-significance (P=0.07) after induction of anesthesia (Figure 9).

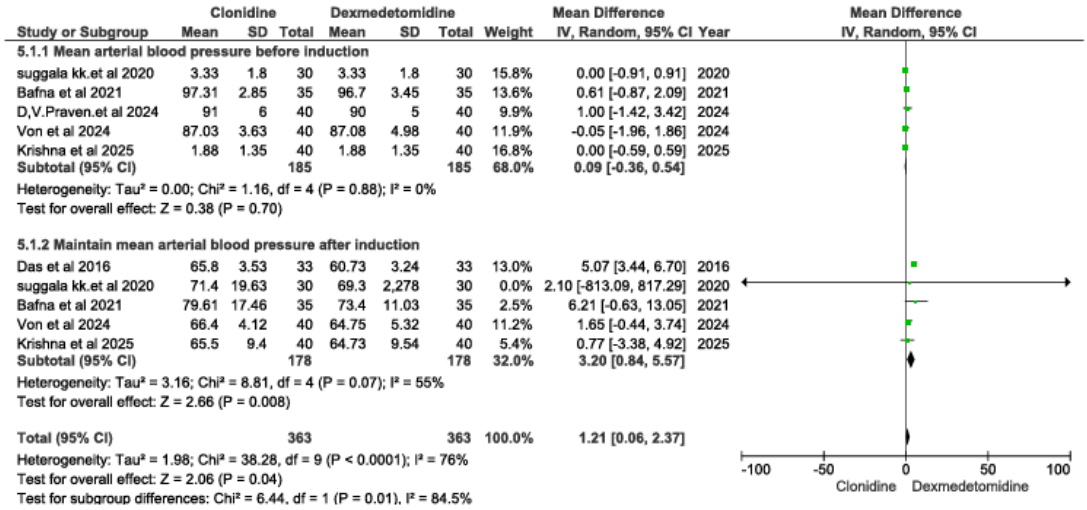

Figure 9. *Forest plot shows comparison of clonidine versus dexmedetomidine on maintenance of mean arterial pressure among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

4.5.7. Clonidine Versus Dexmedetomidine for Maintenance of Heart Rate

Both clonidine and dexmedetomidine have similar effects on the maintenance of heart rate in the normal range before induction (MD = 0.45, 95% CI: -2.11-3.01; p = 0.73). There is moderate heterogeneity among the study group (I^2= 44%) with no statistically significant effect (P=0.15). This study revealed that clonidine is less than dexmedetomidine for maintenance of heart rate in the normal range after induction of anesthesia (MD=2.28, 95% CI: 0.57-3.98; p=0.009). There is low heterogeneity among the study group, I^2=13%, with P=0.13 (Figure 10).

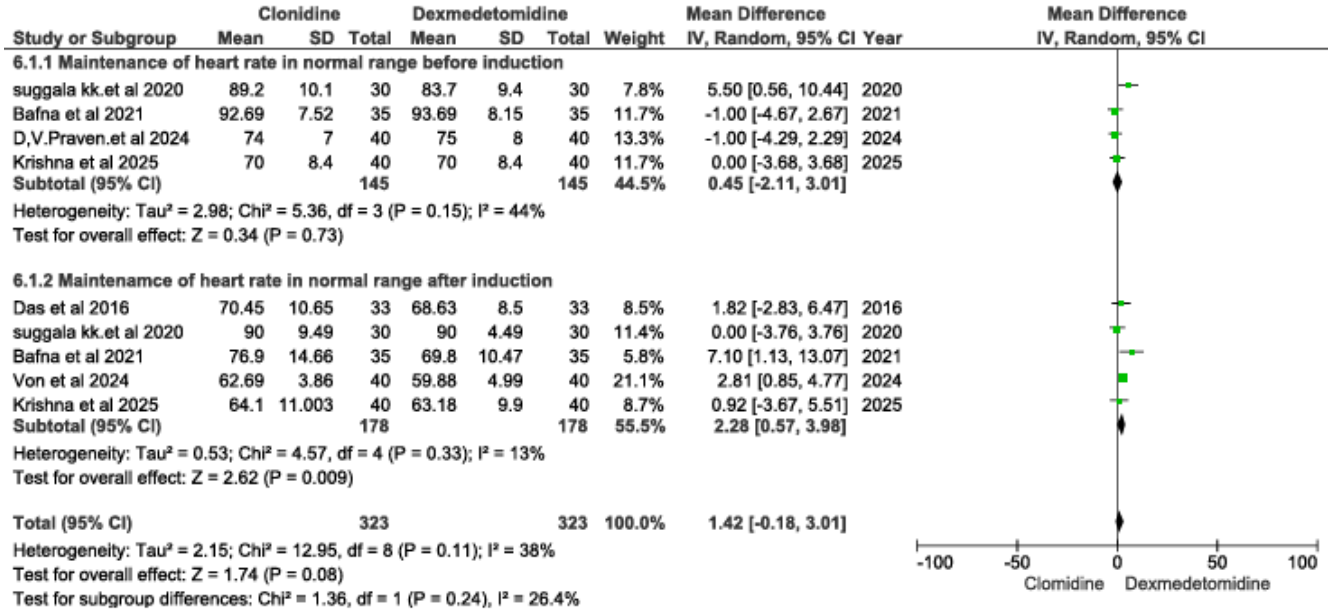

Figure 10. *Forest plot shows comparison of clonidine versus dexmedetomidine on maintenance of heart rate among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

4.5.8. Duration of Surgery

i. Duration of surgery among clonidine versus tranxemic acid

There are only two studies that explain the duration of surgery with clonidine and tranxemic acid. According to this study, patients who take clonidine have longer durations of surgery than patients who have taken tranxemic acid (MD=8.66, 95% CI: -0.04-17.37; p=0.05). There is no heterogeneity between the study group, I ²=0%, P=0.76 (Figure 11).

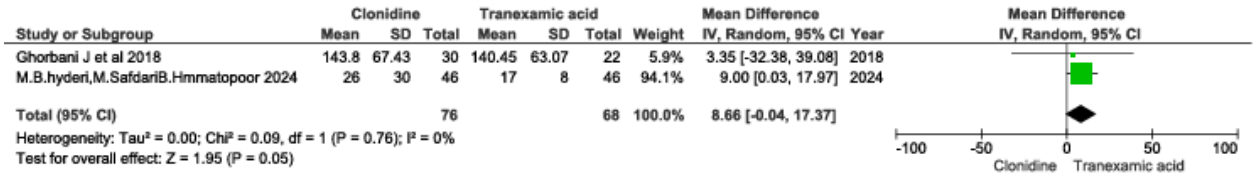

Figure 11. *Forest plot comparison of clonidine and TXA on duration of surgery among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

ii. Duration of surgery among clonidine and placebo

Three studies [12, 13, 24] revealed that clonidine has a shorter duration of surgery than placebo (MD=-11.47, 95% CI: -17.2- -5.74; P<0.0001). There is moderate heterogeneity among the study group, I^2=50%. P=0.13 (Figure 12).

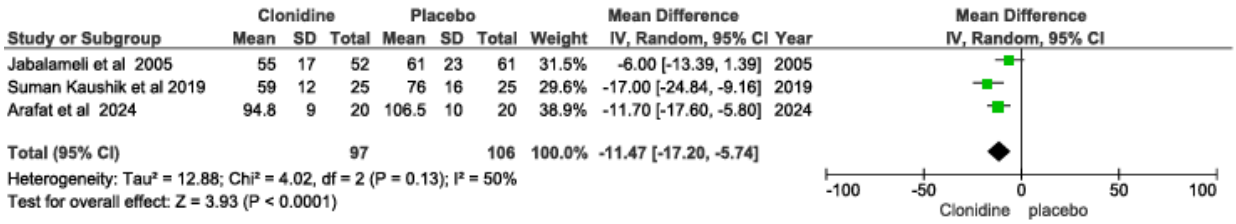

Figure 12. *Forest plot shows comparison of clonidine versus placebo on duration of surgery among adult patients undergoing oral and maxillofacial surgery, 2025.*

iii. Duration of surgery for clonidine versus dexmedetomidine

Clonidine fastens the duration of surgery similarly to dexmedetomidine (MD=1.34, 95% CI: -1.63-4.3; P=0.38). These studies showed that the heterogeneity among the study group is low, I^2=27%, P=0.25 (Figure 13).

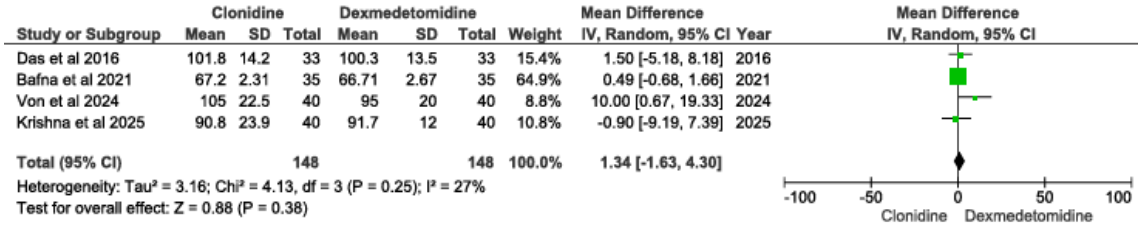

Figure 13. *Forest shows comparison of clonidine versus dexmedetomidine on duration surgery among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

4.5.9. Surgical Field Quality

iv. Surgical field quality of clonidine versus placebo

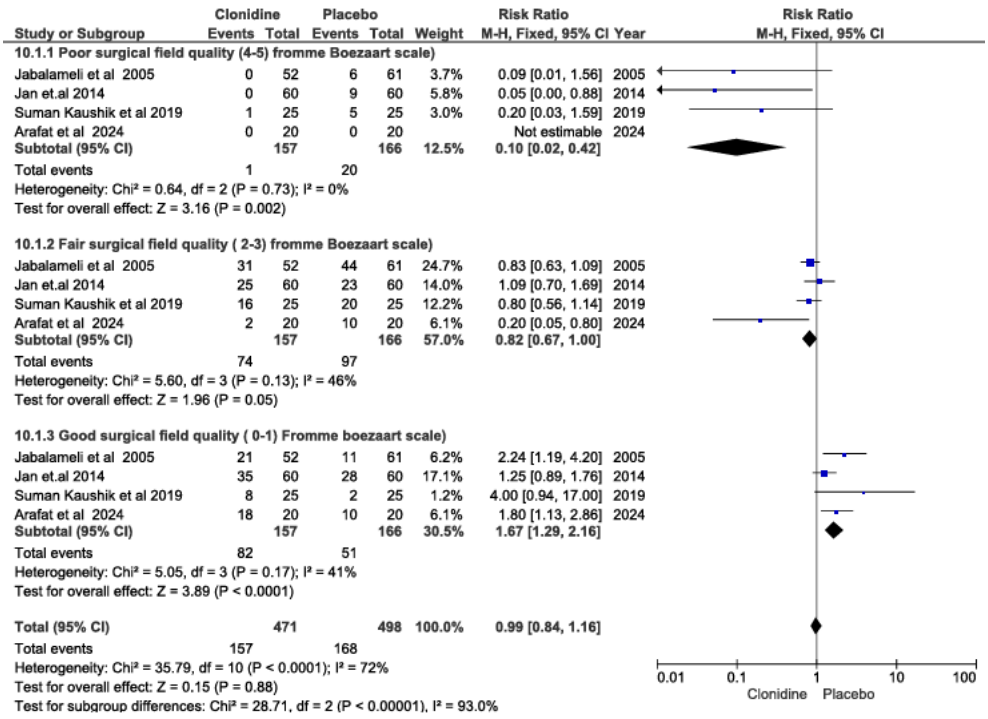

Figure 14. *Forest plot shows comparison of clonidine versus placebo on surgical field quality among adult patients undergoing oral and maxillofacial surgery, 2025.*

Four studies [10, 12, 13, 24] compare the clonidine with the placebo on severe bleeding grade or poor surgical field quality (Boezaart grade 4 and 5). According to this study, patients who take clonidine have less severe bleeding than patients who take a placebo (RR=0.1, 95% CI: 0.02-0.42; p=0.002). No heterogeneity was detected in the study (I^2=0%, p=0.73).

Clonidine has fair surgical field quality or moderate bleeding (Boezaart scale 2 and 3) (RR=0.82, 95% CI: 0.67-1; p=0.05) control more than placebo, but less good surgical field quality than placebo (RR=1.67, 95% CI: 1.29-2.16; p<0.0001). There is moderate heterogeneity for fair surgical field quality and good surgical field quality (I^2=46%, 41%, P=0.13, 0.17), respectively (Figure 14).

Patients who take clonidine have comparable poor surgical field quality (RR=5, 95%, CI: 0.62-40.51; p=0.13) with dexmedetomidine. Heterogeneity was not applicable. Patients who take clonidine have moderate bleeding more than patients who take dexmedetomidine (RR = 1.35, 95% CI: 1.15-1.59; p = 0.0003). There is considerable heterogeneity (I^2 = 81%), with a statistically significant effect (P = 0.001).

Regarding the good surgical field quality (Boezaart scale 0-1), patients who take clonidine have less surgical bleeding than those who take dexmedetomidine (RR=0.45, 95% CI: 0.31-0.67, P<0.0001). There is moderate heterogeneity (I^2=68%) with a statistically significant effect (P=0.002) (Figure 15).

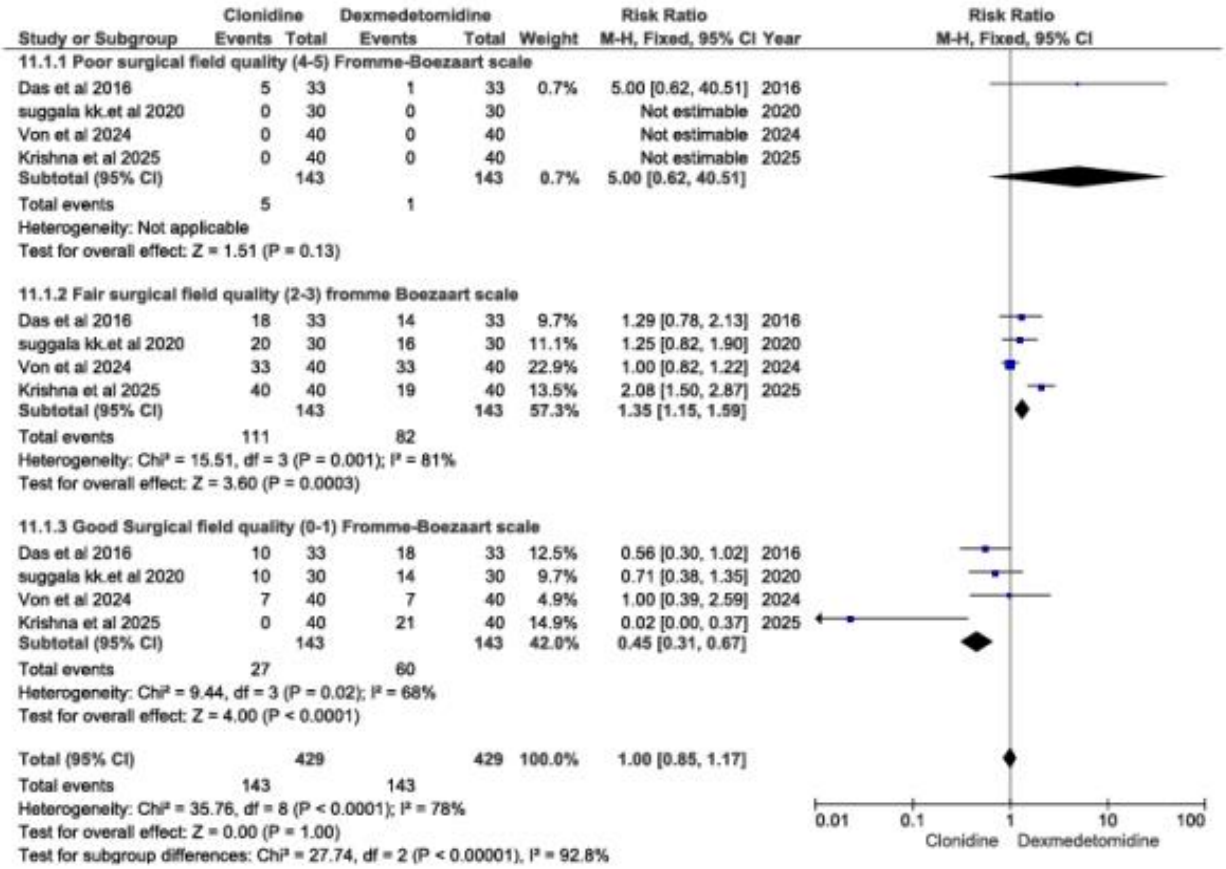

Figure 15. *Forest plot shows comparison of clonidine versus dexmedetomidine on surgical field quality among adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

4.5.10. Adverse Effects of Using Clonidine

Clonidine versus placebo

Hypotension: Patients treated with clonidine have a comparable hypotension effect with placebo (RR=0.9, 95% CI: 0.43-1.9; p=0.78) (Figure 16).

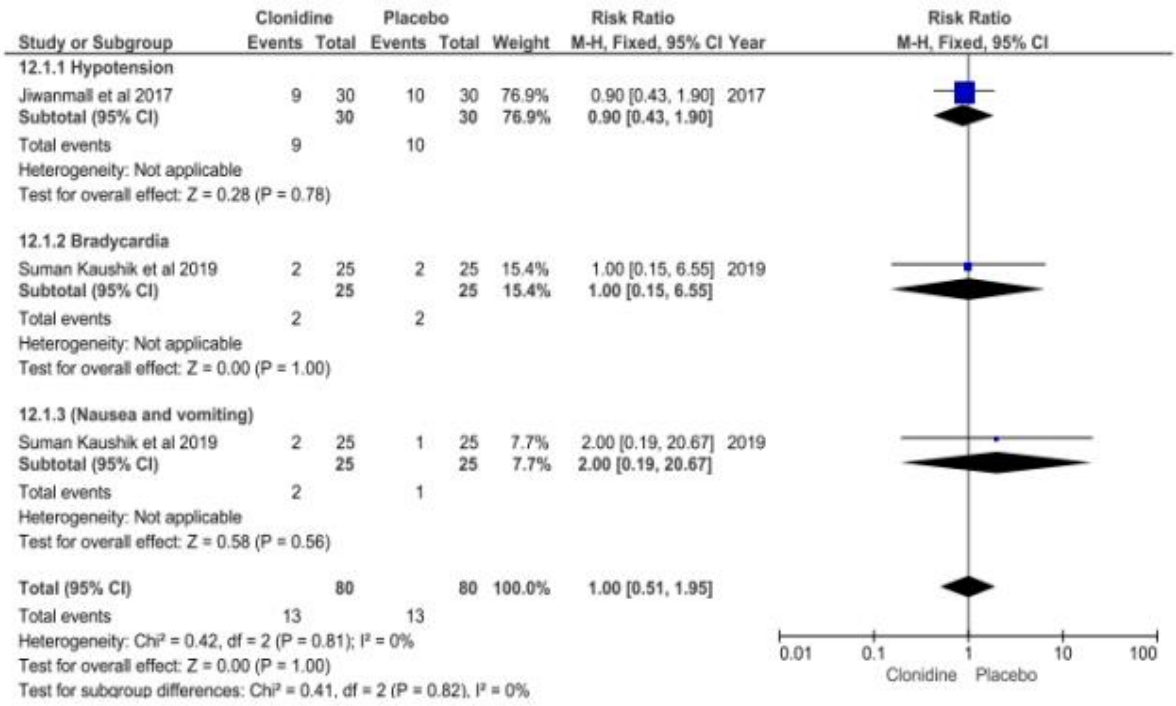

Figure 16. *Forest plot shows comparison of clonidine versus placebo on adverse eventamong adult patients undergoing oral and maxillofacial surgery, SRMA, 2025.*

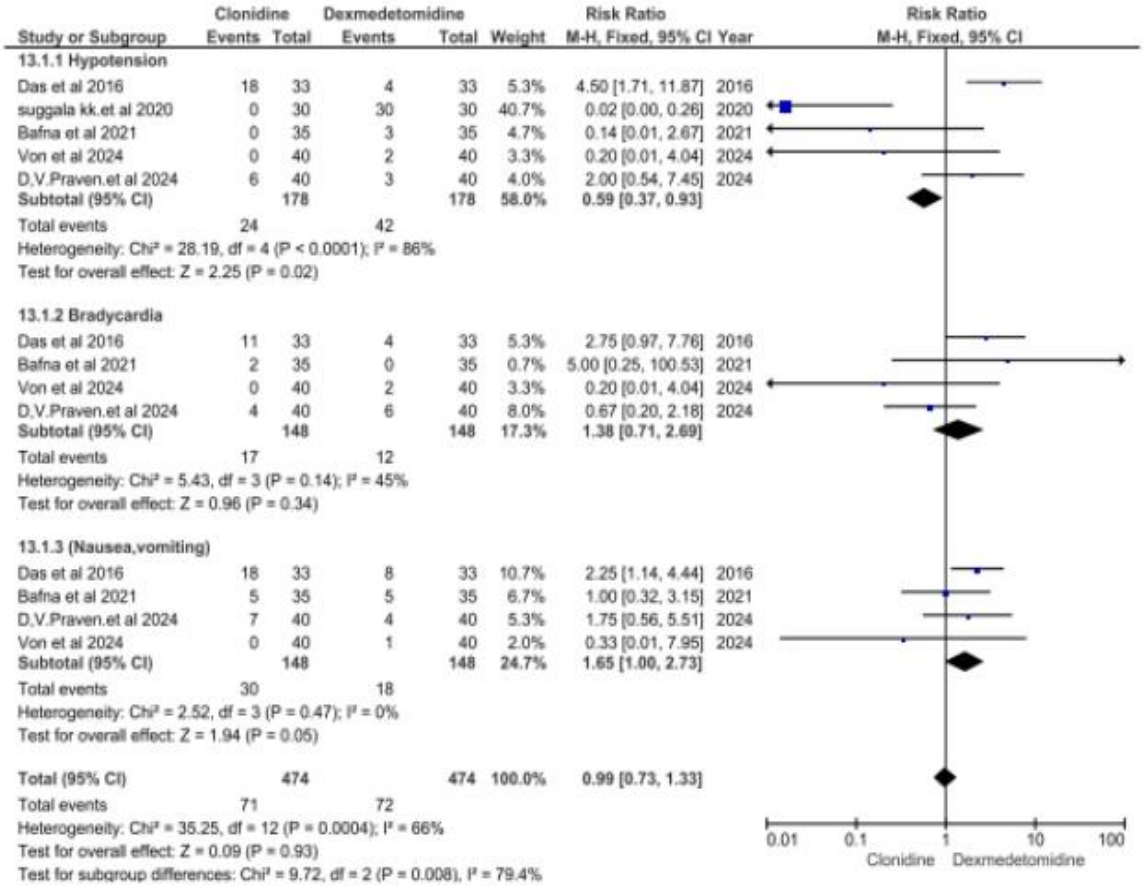

Figure 17. *Forest plot shows comparison of clonidine versus dexmedetomidine regarding to adverse reaction among adult patients undergoing oral and maxilla facial surgery, SRMA, 2025.*

Bradycardia: Clonidine has a similar effect to placebo regarding inducing bradycardia (RR. =1, 95% CI: 0.15-6.55; p=1).

Nausea and vomiting

There is no statistically significant difference between clonidine and placebo regarding induced nausea and vomiting with placebo (RR=2, 95% CI: 0.19-20.67; p=0.56).

Clonidine versus dexmedetomidine

Hypotension: Patients who have taken clonidine have induced hypotension less than patients who have taken dexmedetomidine (RR=0.59, 95% CI: 0.37-0.93; p=0.02). There is high heterogeneity among studies (I^2=86%), with statistical significance (p < 0.0001). There is no statistically significant difference between clonidine and dexmedetomidine for the induction of bradycardia (RR=1.38, 95% CI: 0.71-2.69; p=0.34). There is moderate heterogeneity (I^2=45%), with no statistically significant effect (p=0.14). Regarding the effects of nausea and vomiting when comparing clonidine with dexmedetomidine, the latter has fewer adverse events than the former (RR=1.65, 95% CI: 1-2.73; p=0.05). No heterogeneity was detected (I^2=0%), but it was statistically non-significant (0.47) (Figure 17).

Sensitivity analysis

Sensitivity analysis was conducted by the leave-one-out approach and excluding studies with a high risk of bias for assessing the robustness of the finding. Leave-one-out methods manifested the consistent results for blood loss comparing clonidine with tranxemic acid (MD=0.64, 95% CI: -0.7-1.97, p=0.36, I^2=0%) and surgical field quality, RR=1.13,95%CI: 0.93-1.13, p=0.22, I^2=0%), and removing a single study resulted in changes of overall pooled estimates. While removing a single study doesn't change overall pooled estimates regarding the blood loss comparison of clonidine with dexmedetomidine, the mean arterial blood pressure of clonidine with placebo, and the comparison of clonidine with dexmedetomidine regarding adverse events (Table S6).

4.6. Subgroup Analysis

A post hoc subgroup analysis was performed to determine whether the timing of induction affected the maintenance of MAP. The results showed a statistically significant subgroup effect (Figure 7) (Chi2=4.46, df=1, p=0.03) in which clonidine maintains MAP before induction (MD=-1.88, 95% CI: -3.--0.07; p=0.04) better than after induction (MD=-8.16, 95% CI: -13.7- -2.62; p=0.004). Heterogeneity was not changed after induction (I^2=73%). However, clonidine similarly maintained MAP with dexmedetomidine before induction (MD=0.09, 95% CI: -0.36-0.54; p=0.7); there is a statistically significant difference between subgroup effects (Chi2=6.44, df=1, p=0.01) (Figure 9).

5. Discussion

This systematic review and meta-analysis focused on intraoperative blood loss, hemodynamic stability, and surgical field quality. The measurement clarity for intraoperative blood loss is not standardized in oral and maxillofacial surgery. Hence, our results depend on the study containing measurements of blood loss using different methods [25, 26]. In our meta-analysis the amount of blood loss is mean and standard deviation (71±16.39 to 548.8±99.5) with an overall effect of 40.17 in clonidine with tranxemic acid. But this is reduced to 0.64 after sequential removing of one study [8].

Our findings indicate that clonidine is reducing bleeding more than placebo (MD = -75.15, 95% CI: -96.04 to -54.25; P < 0.00001) and less than dexmedetomidine (MD = 76.5, 95% CI: 1.19-14.11; P = 0.02 MD=-1.88, 95% CI: -3.--0.07; p=0.04). There was insufficient evidence for the reduction of bleeding of clonidine with tranxemic acid. A sensitivity analysis test revealed that clonidine is better at reducing blood loss than dexmedetomidine and good for improving surgical field quality (poor surgical field quality) and (fair surgical field quality) comparable to dexmedetomidine. Clonidine is at higher risk of hypotension and nausea and vomiting than dexmedetomidine.

A subgroup analysis showed that clonidine maintained mean arterial blood pressure before induction better than after induction when compared with placebo (MD=-1.88, 95% CI: -3.7--0.07; p=0.04) but similar to dexmedetomidine before induction. Clonidine maintained mean heart rate in the normal range before and after induction, similar to placebo but comparable to dexmedetomidine only before induction.

In our study, clonidine is less controlling blood loss than with tranxemic acid. This is in line with M. B. Hyderi, M. Safdari, and Hemmatpoor [8] reported the superiority of tranxemic acid, in contrast to this the study by Akraham et a. [9] and Zara et al. [27]. demonstrated the superiority of clonidine in reducing blood loss The study by Ghorbani J et al. [7]. which reported that clonidine has a similar effect to tranxemic acid on reducing blood loss during functional endoscopic sinus surgery. The pooled results showed that patients who take clonidine have better blood loss control than those who don't take clonidine but less blood loss control than those who take dexmedetomidine. This is in line with a systematic review by Bhatas and Pariasamy [26] and randomized controlled trials by Jan et al. [10], Suman Kaushik et al. [12] which reported that clonidine decreases blood loss more than placebo. Our study is in concordance with the study by Das et al. [16], D. V. Praveen et al. [20] and Krishna et al. [22] which explained dexmedetomidine is controlling blood loss than clonidine. But it is contrast with Study by Von et al. [28], Suggala KK et al. [17] and Bafina et al. [18] reported that clonidine is comparable with dexmedetomidine for blood loss control.

5.1. Strength and Limitation of the Study

This study is the first meta-analysis that reported the effect

of clonidine on intraoperative blood loss control, hemodynamic stability, surgical field quality, and duration of surgery in oral and maxillofacial surgery. This study enhances the effectiveness of clonidine, as it is cheap and especially useful in resource-limited areas for controlling blood loss. It applies to adult patients from age 18 to 75 years, ASA-1 and II from all ethnic groups, who are undergoing oral and maxillofacial surgery. This review and meta-analysis have the following limitation, so we suggest caution during interpretation and use. 1. High heterogeneity. 2. Sample size comparison: Some studies are small; this may lead to publication bias and downgrade the certainty of evidence. 3. Almost all of the studies are conducted on the same continent, except for two, which are conducted in Africa, and the included studies only have mild systematic disease (ASA-I and ASA-II), which leads to decreased generalizability of evidence. 4. The high risk of bias included studies [7, 9, 12, 13, 15, 22] reduces reliability of evidence. 5. Vasoconstriction use before intubation and skin infiltration before surgery may lead to overestimation or underestimation of hemodynamic measurements.

5.2. Implication and Future Directives

This review and meta-analysis put points for future research. Comparison of clonidine with tranxemic acid on blood loss concluded with the superiority of tranxemic acid. While there are studies showing clonidine has more blood loss control than tranxemic acid. This disparity will be addressed by additional careful trials to minimize confounding. Future investigators will be focused on the dose and timing of administration when comparing clonidine with placebo and dexmedetomidine.

6. Conclusion

This systematic review and meta-analysis concluded that clonidine is decreased blood loss than placebo by 75ml. The meta-analysis revealed extreme statistical heterogeneity in the comparison of clonidine with tranxemic acid, suggesting substantial inconsistency in treatment effects across studies. Clonidine is less likely to be inferior to dexmedetomidine in reducing blood loss for oral and maxillofacial surgery.

Subgroup analysis showed that clonidine maintained mean arterial blood pressure in a normal range better than placebo when administered pre-induction than after induction. Though clonidine is comparable with placebo, post-induction clonidine administration maintains a lower mean heart rate than placebo. Clonidine is maintained MAP before induction, and it is effective pre-induction than post-induction administration to maintain a mean heart rate in normal range with dexmedetomidine. Clonidine is a fast-acting duration of surgery comparable with tranxemic acid and dexmedetomidine but more than placebo.

Clonidine decreases the risk of severe bleeding by 10% than placebo but is similar to dexmedetomidine. Clonidine reduces hypotension by 59% more than dexmedetomidine. Clonidine is not significantly different from placebo regarding the risk of induced hypotension, bradycardia, and nausea and vomiting. However, this requires caution due to high heterogeneity. It is comparable to dexmedetomidine for bradycardia but at risk for nausea and vomiting.

Abbreviations

Dex	Dexmedetomidine
GRADE	Grade of Recommendation, Assessment, Development and Evaluation
IV	Intravenous
MAP	Mean Arterial Blood Pressure
MD	Mean Difference
MHR	Mean Heart Rate
NS	Normal Saline
PRISMA	Protocol of Systematic Review of Meta-Analysis
PICO	Population, Intervention, Comparator, Outcome
RR	Relative Risk
RCT	Randomized Controlled Trial
SRMA	Systematic Review and Meta-analysis
TXA	Tranxemic Acid

Supplementary Material

The supplementary material can be accessed at https://doi.org/10.11648/j.sdmed.20260102.12

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Simon Mengistu Feye: Formal analysis, Supervision, Validation, Writing – original draft

Kelil Musa Nerso: Data curation, Funding acquisition, Investigation, Visualization

Dinku Tsegaye Urji: Data curation, Validation, Visualization

Ebrahim Ahmed Hussen: Investigation, Validation, Writing – review & editing

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Conflicts of Interest

The authors declare no conflicts of interest.

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