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Effectiveness of clonidine as a preanesthetic drug on intra operative blood loss in oral and maxillofacial surgery: A systematic review

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***Abstract*---**Controlled hypotension during a surgical procedure is a way to decrease blood pressure and subsequently to improve the field of operation. Clonidine is an antihypertensive drug which acts through facilitation of Alph-2 post-synaptic receptors and in addition to its antihypertensive, anti-anxiety and analgesic effects, its beneficial effects in reducing the bleeding during. Correction of maxillomandibular discrepancies may necessitate performing osteotomy on both the jaws in several cases. Bimaxillary orthognathic surgery and rhinoplasty are procedures associated with significant blood making proper hemostasis essential for a surgical field that is free of excessive blood, reduced postoperative swelling, and appropriate surgical results. The aim of this systematic review is to assess the effectiveness of Clonidine as a pre-anesthetic drug on intraoperative blood loss in maxillofacial surgery. The Databases of PubMed, Cochrane and Google scholar were searched for the related topics along with a complimentary manual search of all oral surgery journals till January 2021. Articles were selected based on the inclusion criteria, which included all RCTs. From this study it is concluded that clonidine premedication is effective in reducing intraoperative blood loss as well as providing hemodynamic stability in patients undergoing different maxillofacial surgeries. Clonidine is effective in achieving controlled hypotension in patients various surgeries of the head and neck. It reduces intraoperative blood loss, requirement of additional hypotensive drugs, improves the surgical field and offers good analgesia without significant side effects.

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Keywords---oral clonidine, intraoperative blood loss, maxillofacial surgery, surgical field, hypotensive.

Introduction

Bleeding during various maxillofacial surgeries remains a challenge for both surgeons and anesthesiologists despite several modalities available for improving the surgical field. However, as the orofacial region is very vascular, significant blood loss can occur and a subsequent need for blood transfusion is often encountered (1). Adverse effects of blood transfusion include transmission of infectious disease, immunosuppression, and incompatibility reactions (2). Deliberate lowering of blood pressure is used as an aid to surgery to produce a bloodless surgical field (3,4). It has been reported to reduce total blood loss by as much as 40% and improve the surgical field by 27% in orthognathic surgery (5). Clonidine, an imidazole compound, is an established antihypertensive agent, which appears to act mainly by central alpha-2 adrenoreceptor stimulation, resulting in diminished sympathetic outflow. It has been shown to have sedative and analgesic properties, to suppress stress-induced central noradrenergic hyperactivity, to decrease anesthetic requirements, to attenuate reflex cardiovascular response to tracheal intubation, and to improve hemodynamic stability during surgery (6,7).

Prolonged surgery is one of the upcoming results of bleeding during the surgery which cause an increase in the surgeon's fault because of the edema following a prolonged operation. Clonidine has been administered to provide hemodynamic stability during the perioperative period (8) . The main routes used preoperatively are the oral and epidural routes. Oral clonidine has been shown to decrease the need for analgesia during and after surgery under general anesthesia (9). A study done previously, suggested 150 micrograms of clonidine, given orally 90 min preoperatively, is an effective premedication in dentistry, without causing excessive haemodynamic depression and sedation, and moreover confirm that the oral route of administration is very well accepted (10).

Clonidine premedication augments the pressor and tachycardiac responses to ephedrine (11). Procedures like Rhinoplasty and bimaxillary orthognathic surgeries are common aesthetic procedures that are associated with excessive blood loss. Proper homeostasis is quintessential for a surgical field that is free of excessive blood, reduced postoperative swelling, and appropriate surgical results. Previously our team has a rich experience in working on various research projects across multiple disciplines (12–26) Now the growing trend in this area motivated us to pursue this project.

Aim

The aim of this systematic review is to assess the effectiveness of Clonidine as a pre-anesthetic drug on intraoperative blood loss in maxillofacial surgery

Structured question

Is Clonidine as a pre anesthetic drug effective in lowering intraoperative blood loss following oral and maxillofacial surgery.

PICO analysis

- Population: Patients undergoing different maxillofacial procedures
- Intervention: Clonidine
- Comparison: Placebo, Normal saline
- Outcome: Intraoperative blood loss, Quality of surgical field

Materials and Methods

Search methodology

#6	•••	>	Search: **maxillofacial osteotomy surgery**	6,634	09:26:16
#5	•••	>	Search: **Orthognathic sugery**	3	09:26:03
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#24	•••	›	Search: **Placebo**	238,354	09:30:40
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#20	•••	›	Search: **Injection clonidine**	3,098	09:29:43
#19	•••	›	Search: **Clonidine**	18,386	09:29:32
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#15	•••	›	Search: **Dentoalveolar surgery**	1,373	09:28:13
#14	•••	›	Search: **Midface fracture**	701	09:28:03
#13	•••	›	Search: **Mandibular fracture**	10,349	09:27:23
#12	•••	›	Search: **Maxillary fracture**	5,042	09:27:14
#11	•••	›	Search: **Jaw surgery**	23,315	09:27:06
#10	•••	›	Search: **Lefort I osteotomy**	385	09:26:57
#9	•••	›	Search: **mandibular osteotomy**	6,350	09:26:46
#8	•••	›	Search: **maxillary osteotomy**	4,052	09:26:38
#7	•••	›	Search: **bimaxillary osteotomy**	806	09:26:28
#6	•••	›	Search: **maxillofacial osteotomy surgery**	6,634	09:26:16

History and Search Details

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Search	Actions	Details	Query	Results	Time
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#29	•••	›	Search: **Blood loss**	556,838	09:31:30
#28	•••	›	Search: **haemorrhage**	5,000,006	09:31:20
#27	•••	›	Search: **bleeding**	531,616	09:31:10
#26	•••	›	Search: **(Placebo) OR (Normal saline)**	300,019	09:30:59
#25	•••	›	Search: **Normal saline**	65,325	09:30:50

Advanced Search

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#1	Oral surgery	S	MeSH	Limits	29587
#2	maxillofacial surgery			Limits	3964
#3	Dental surgery			Limits	7047
#4	Orthognathic surgery			Limits	543
#5	maxillofacial osteotomy surgery			Limits	392
#6	bimaxillary osteotomy			Limits	59
#7	maxillary osteotomy			Limits	252
#8	mandibular osteotomy			Limits	323
#9	Lefort I osteotomy			Limits	27
#10	Jaw surgery			Limits	1552
#11	Maxillary fracture			Limits	266
#12	Mandibular fracture			Limits	453
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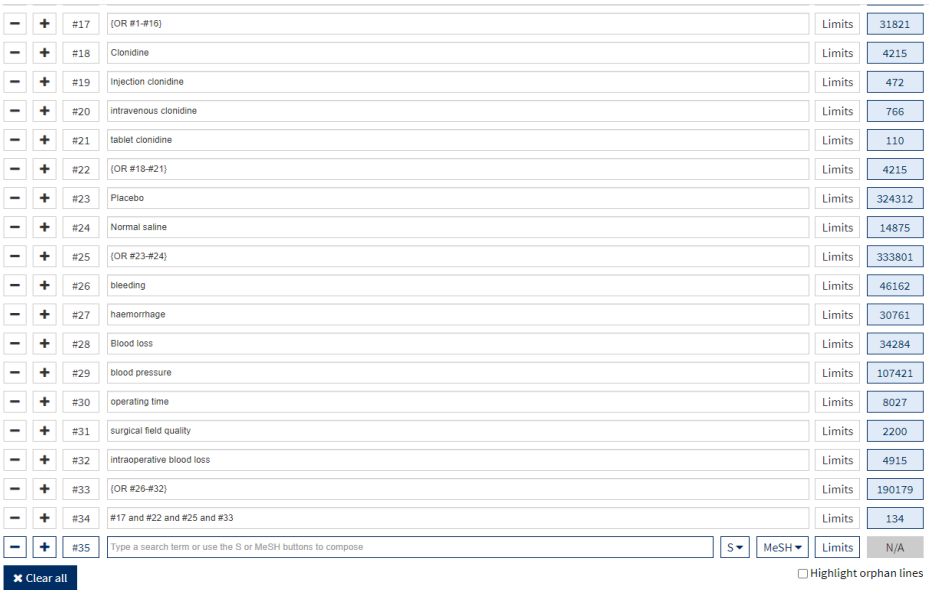

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#23	Placebo	Limits	324312
#24	Normal saline	Limits	14875
#25	{OR #23-#24}	Limits	333801
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#27	haemorrhage	Limits	30761
#28	Blood loss	Limits	34284
#29	blood pressure	Limits	107421
#30	operating time	Limits	8027
#31	surgical field quality	Limits	2200
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#34	#17 and #22 and #25 and #33	Limits	134
#35	Type a search term or use the S or MeSH buttons to compose	S MeSH Limits	N/A

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Inclusion criteria

Criteria for considering studies for the Review –

- Types of studies -
  - Randomized controlled trials
  - Clinical trials.
- Types of Participants –
  Patients undergoing maxillofacial surgery
- Types of Intervention
  Intraoperative blood loss is evaluated using clonidine as a pre anaesthetic drug for the patients undergoing different maxillofacial procedures
- Types of Comparison
  Intraoperative blood loss is evaluated using placebo for the patient undergoing maxillofacial surgery.
- Types of Outcome Measures
  Intraoperative blood loss was evaluated using preweighed gauze pieces for the patient undergoing maxillofacial surgery.

Exclusion criteria

The following studies were excluded,

- Review articles
- Animal studies
- Invitro studies
- Studies not meeting inclusion criteria
- Languages other than English

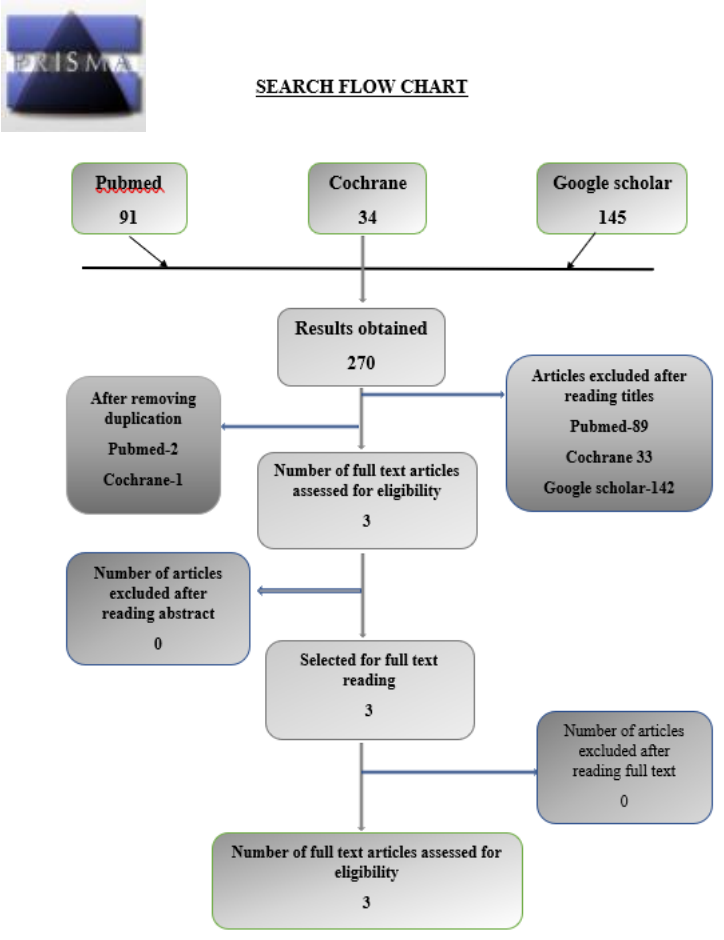
Sources used

The Data Bases of PubMed, Cochrane and Google scholar were searched for the related topics. We used free-text terms to search the following journals"

- British Journal of Oral and Maxillofacial Surgery
- International Journal of Oral and Maxillofacial Surgery
- Journal of Oral and Maxillofacial Surgery
- Journal of Cranio Maxillofacial Surgery
- Quintessence International Journal

Only articles in English and human species were applied during the electronic search to include all the possible clinical trials that are relevant for the search phase of the systematic review. Reference list of the identified randomized trials were also checked for possible additional studies.

PRISMA 2009 flow diagram



Data collection and analysis
Screening and selection

Electronic search was carried out using the keywords in the Search engines- PubMed, Cochrane and Google Scholar which yielded a total of 227 articles. Based on pre-set inclusion and exclusion criteria, the titles of the studies identified from the search were assessed independently by two review authors (Dr .Swetha Bhat, Prof.Dr. Senthilnathan Periasamy). Conflicts concerning inclusion of the studies were resolved by discussion. Two hundred and nineteen articles were excluded after reading titles. Four titles were identified from the search after excluding Four duplication. Abstracts of selected articles were reviewed independently. No articles were excluded after reading abstract. Full text articles were retrieved for four relevant studies. The reference list of the full text articles were reviewed for identifying additional studies. Titles of articles relevant to the review were selected by discussion. Quality Assessment criteria to evaluate the studies were decided by two review authors in accordance with CONSORT guidelines. The risk of bias for each study was independently assessed by the review authors and conflicts concerning risk of bias were sorted by discussion.

Data extraction

Data extraction for general characteristics of studies and variables of outcome was done. For each trial the following data were recorded:

- Author and Journal
- Study Design
- Sample Size
- Participants and Group
- Methodology
- Outcome measures
- Results
- Conclusion

Table1
Variables of interest

S.No	VARIABLES OF INTEREST
1.	Intraoperative blood loss

Quality assessment

(Higgins and Green. Cochrane reviewer's hand book 2009). The quality assessment of included trials was undertaken independently as a part of data extraction process. Four main quality criteria were examined.

1. Method of Randomization, recorded as
   a) YES- Adequate as described in the text
   b) NO- Inadequate as described in the text

c) Unclear in the text
2. Allocation Concealment, recorded as
a) YES- Adequate as described in the text
b) NO- Inadequate as described in the text
c) Unclear in the text
3. Outcome assessors Blinded to intervention, recorded as
a) YES- Adequate as described in the text
b) NO- Inadequate as described in the text
c) Unclear in the text
4. Completeness of Follow up (was there a clear explanation for withdrawals and dropouts in each treatment group) assessed as
a)YES- Dropouts were explained
b) NO- Dropouts were not explained
c) None- No Dropouts or withdrawals.

Other methodological criteria examined included:
1. Presence or Absence of sample size calculation.
2. Comparability of Groups at the start.
3. Clear Inclusion or Exclusion criteria.
4. Presence or Absence of estimate of measurement error.

Risk of bias in included studies

The study was assessed to have a “High risk” of bias if it did not record a “Yes” in three or more of the four main categories, "Moderate Risk "if two out of four categories did not record a "Yes", and “Low Risk” if all the four categories recorded if randomization assessor, Blinding and Completeness of follow up were considered Adequate. In case of non-randomized and clinical trials without control group, it is recorded as not applicable.

Results

Table 2
General characteristics of the studies

S. No	Author	Year	Study design	Sample size	Age	Technique Used	Method of Evaluation
1	Mohammadi et al	2016	Randomised double blinded clinical study	N=30	18-40 yrs	One group receiving Clonidine and another group receiving placebo	Intraoperative blood loss was evaluated by counting soaked gauze pads Evaluation of operating time
2	Ghazipour et	2013	Randomis	N=80	Mean	One group	Intraoperativ

	al		ed double blinded clinical study		age-22.5 yrs	receiving clonidine and another group receiving placebo	e blood loss graded in 4 groups according to amount of contaminatio n of the surgical gauze pad with blood Evaluation of operating time
3.	Tabrizi et al	2014	Randomis ed uni-blinded clinical study	N=66	18 - 35 yrs	One group receiving clonidine and another group receiving placebo	Intraoperativ e Blood loss was determined by the accumulatio n of blood in a surgical suction unit and weight of a pre-weighed soaked gauze pad Evaluation of operating time - the first incision through closure of the incisions

Table 3
Data extraction table

S.no.	Author and year	Technique used	Method of evaluation	Mean values	Outcomes
1.	Mohammadi et al, 2016	One group receiving pregabalin and another group receiving placebo	Intraoperative blood loss was evaluated by counting soaked gauze pads Evaluation of operating time	Intraoperative blood loss Clonidine group= 287.33 ± 72.06 mL Placebo group= 508.67 ± 46.2 mL Operation time (min)	Intraoperative blood loss and operating time in Clonidine group was significantly less

				Clonidine group= 166 ± 7.1 Placebo group=176 ± 8.52	
2.	Ghazipour et al, 2013	One group receiving pregabalin and another group receiving placebo	Intraoperative blood loss graded in 4 groups according to amount of contamination of the surgical gauze pad with blood Evaluation of operating time	Intraoperative bloodloss Number of patients with Bleeding grade I Clonidine -17 Placebo- 12 Bleeding grade II Clonidine -13 Placebo- 17 Bleeding grade III Clonidine -9 Placebo- 3 Bleeding grade IV Clonidine -1 Placebo- 8 Operating time (min) Clonidine group= 62 ± 10 Placebo group=70 ± 12	Intraoperative blood loss and operating time in Clonidine group was significantly less
3.	Tabrizi et al, 2014	One group receiving pregabalin and another group receiving placebo	Intraoperative Blood loss was determined by the accumulation of blood in a surgical suction unit and weight of a pre-weighed soaked gauze pad Evaluation of operating time - the first incision through closure of the incisions	Intraoperative blood loss Clonidine group= 68.03 ± 22.49 mL Placebo group= 132.12 ± 78.53 mL Operating time (min) Clonidine group= 1.24± 0.48 Placebo group=1.21 ± 0.45	Intraoperative blood loss in Clonidine group was significantly less Operating time showed no significant difference (P<0.05)

Table 4
Evidence level of selected articles

SI No	Author and year	Study design	Level of Evidence
1	Mohammadi et al, 2016	Randomised double blinded study	1b
2	Ghazipour et al, 2013	Randomised double blinded study	1b
3	Tabrizi et al, 2014	Randomised uni-blinded clinical study	1b

Table 5
Risk of bias- major criteria

S.No	Study	Randomization	Allocation concealment	Assessor Blinded	Drop outs described	Risk of Bias
1	Mohammadi et al, 2016	Yes	Yes	Yes	None	Moderate
2	Ghazipour et al, 2013	Yes	No	Yes	Yes	Moderate
3	Tabrizi et al, 2014	Yes	No	Yes	No	Moderate

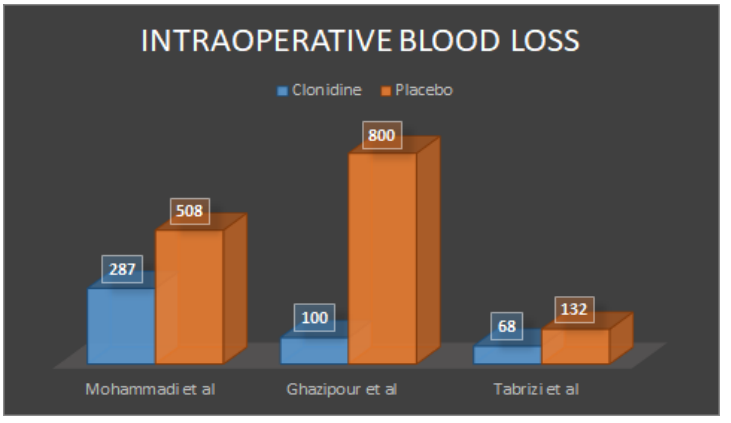
Table 6
Risk of bias-minor criteria

S.No	STUDY	SAMPLE JUSTIFIED	BASELINE COMPARISON	I/E CRITERIA	METHOD OF ERROR
1	Mohammadi et al, 2016	No	Yes	Yes	No
2	Ghazipour et al, 2013	No	Yes	Yes	No
3	Tabrizi et al, 2014	No	Yes	Yes	No

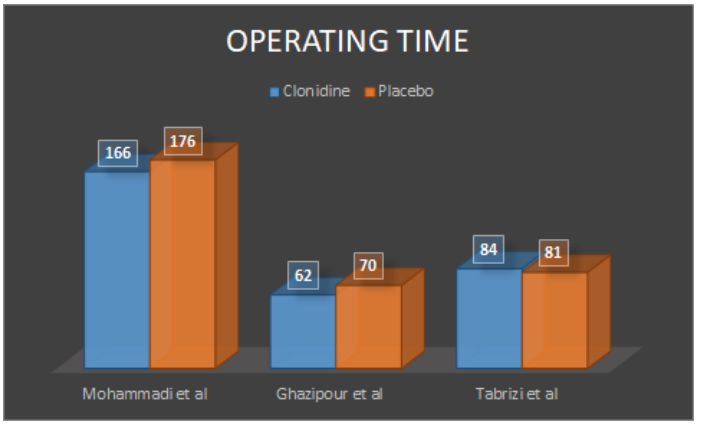
Table 7
Summation table for individual parameter

S.No	Author	Year	Evaluation period	Outcome
1	Mohammadi et al	2016	Intraoperative evaluation	There was significant difference between two groups, results are in favour of Clonidine group
2	Ghazipour et al	2013	Intraoperative evaluation	There was significant difference between two groups, results are in favour of Clonidine group
3	Tabrizi et al	2014	Intraoperative evaluation	There was significant difference between two groups, results are in favour of Clonidine group

Graph 1 Comparison of post operative pain



Graph 2 Comparison of operating time



Discussion

For any elective surgical procedures, hemodynamic stability, dry field of surgery, decreased blood loss during the procedure, and increased satisfaction of surgeon and anesthesiologist are of the utmost importance. There are various methods for controlling the bleeding during the surgery, such as elevation of the head over the trunk during the operation, injection of the diluted solution of Epinephrine in the incision site and osteotomy site and also blood pressure control during the surgery (27). Occurrence of this problem depends on many variables concerning the patient, surgical conditions and anesthesia. Over the past few decades the strategy of lowering patient's blood pressure during anesthesia or "Hypotensive anesthesia" has been practiced to reduce the blood loss during surgeries (28–31) . A natural survival mechanism is what lies as a physiological principle behind hypotensive anesthesia. During profuse bleeding the blood pressure drops which inturn leads to reduction of bleeding, blood pressure stabilization and recovery. Likewise intentionally reducing the blood pressure during surgery can reduce overall bleeding (32)

Clonidine is an antihypertensive drug with a central effect on Alpha-2 receptors and has been used as a premedication for reducing pain and also nausea and vomiting and tremor after surgery. It has also been given orally as an adjunct to augment the hypotensive action during the surgery. This drug performs its antihypertensive effect through reduction in sympathetic outgoing potential (33). Clonidine has been found to suppress central noradrenergic hyperactivity with a secondary attenuation of perioperative hemodynamic instability (34)**.** Many studies have proved the use of clonidine as a premedication in reducing the blood loss during various surgeries like middle ear surgery, neurosurgery, sinus endoscopic surgeries and orthopedic surgeries (35–39). The purpose of this systematic review was to find out the efficiency of clonidine administered before various surgeries of the maxillofacial region to reduce the intraoperative blood loss during the surgery. So far, there have been three studies that have evaluated the effect of premedication with clonidine on reducing the intraoperative bleeding during maxillofacial surgeries (40–42). Our institution is passionate about high quality evidence based research and has excelled in various fields (16,43–52)

Interpretation of results

According to Mohammadi et al (2013), a total of 30 participants who were candidates for double-jaw orthognathic surgery under general anesthesia were equally divided into 2 groups. The study reports that patients of group 1 who received 300 mg oral clonidine premedication was administered 90 min before the induction of anesthesia were found to have reduced blood loss during the surgical procedure of double jaw orthognathic surgery when compared to the patients of group 2 who received a placebo drug before the induction of general anesthesia. In addition significant differences were observed in operation time ($P < 0.05$) and surgeon satisfaction ($P < 0.001$). According to Ghazipour A et al (2014), 80 patients who required open rhinoplasty under general anesthesia were equally divided into 2 groups. This study reports that patients of group 1 who received oral clonidine in the dosage of 5µg/kg, 60 minutes before the induction of general anesthesia were found to have a reduced blood loss during the surgical procedure

of rhinoplasty when compared to the patients of group 2 who received a placebo drug before the induction of general anesthesia. However in this study there was no significant reduction was observed between the patients of group 1 and group 2 with respect to mean arterial blood pressure.

According to Tabrizi R. et al (2013), 66 patients who required open rhinoplasty under general anesthesia were equally divided into 2 groups. The study reports that patients of group 1 who received oral clonidine (0.2 mg) 2 hours before the induction of anesthesia were found to have reduced blood loss during the surgical procedure of rhinoplasty when compared to the patients of group 2 who received a placebo drug before the induction of general anesthesia. In addition the study also reports a significant reduction in the systolic and diastolic blood pressure in the group 1 patients (clonidine) when compared to the patients of group 2 (placebo).

Implication for practice

Clonidine, as a single bolus dose, is effective in achieving controlled hypotension when used with balanced anaesthesia in Oral and maxillofacial sugery and reduces the intraoperative requirement of additional fentanyl and metoprolol. It effectively reduces the intraoperative blood loss and provides a dry operating field. Clonidine also provides good analgesia without any significant side effects such as sedation, hypotension and bradycardia. Use of clonidine for controlled hypotension is simple, safe and cheap, which makes economic sense for developing and developed countries. Further studies on effect of clonidine on perioperative platelet reactivity are needed to furthermore establish this fact.

Implication for research

Further studies which compare the effect of oral clonidine with other drugs and studies comparing the effect of clonidine through other routes of administration will determine the best drug and route of administration to reduce the intraoperative bleeding during various maxillofacial surgeries. Whether the use of these drugs is feasible in terms of health economics also should be studied.

Summary

The aim of this systematic review is to assess the effectiveness of Clonidine as a pre anaesthetic drug on intraoperative blood loss in maxillofacial surgery. There were 3 randomised controlled trails included in this systematic review. The studies have used 300 mg, 5µg/kg and 0.2 mg of clonidine respectively. Assessment of the intraoperative blood loss during the surgical procedure and reduction in operating time were the variables of interest. The results of this systematic review provides a basis for administration of clonidine as a premedication can be effectively used as an adjunct to hypotensive anesthesia to augment the effect of hypotension and reduce the bleeding as well as operating time during surgery.

Conclusion

From this systematic review it can be concluded that administration of clonidine as a premedication in patients undergoing maxillofacial surgeries effectively reduces the intraoperative blood loss during the surgical procedure which may contribute in achieving good results. Further studies with a larger sample size and studies which evaluate other parameters such as quality of surgical field and operator satisfaction are necessary to collaborate the findings of the present study for their wider use in clinical practice.

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