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Effect of premedication with oral clonidine on intraoperative blood loss during rhinoplasty surgery - A systematic review

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ABSTRACT

Rhinoplasty is one frequent surgical procedure of many technical variations that only a few surgeons are considered to have mastered its broad scope. Operative site bleeding is considered to be an exasperating issue in the surgical procedure of rhinoplasty. Over the past few decades, the strategy of lowering patient's blood pressure during anaesthesia or "Hypotensive anaesthesia" has been practised to reduce the blood loss during surgeries. Clonidine is an antihypertensive drug and is suggested to have advantageous effects in controlling the intraoperative blood loss. The objective of this systematic review was to explore and study the existing literature and determine the efficacy of oral clonidine as a premedication in reducing the intraoperative blood loss in rhinoplasty surgeries. Data was gathered from electronic databases like PubMed, Medline and Cochrane central library. An additional manual search was performed with various journals to look for available articles to include in the systematic review. Only those studies which met the criteria for inclusion were selected. All studies and reports that evaluated oral clonidine with placebo in reducing bleeding during rhinoplasty surgery were included. Pertinent literature abstracts and full-text articles pertaining to the query were analysed. Two articles in total were taken in for qualitative analysis, both of which were randomised clinical trials. Oral clonidine shows significantly more efficient in reducing intraoperative bleeding than the placebo group. Premedication with oral clonidine is significantly effective in controlling blood loss during the surgical procedure of rhinoplasty.

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INTRODUCTION

Rhinoplasty is one frequent surgical procedure of many technical variations that only a few surgeons are considered to have mastered its broad scope (Tardy and Brown, 1997); (Rohrich *et al.*, 2014). Rhinoplasty has evolved considerably during the last decade from a standardised reduction procedure to a highly differentiated problem-oriented surgical procedure where a combination of reduction, relocation and augmentation of tissues are performed (Sheen, 2000) . Operative site bleeding is considered to be an exasperating issue in the surgical procedure of rhinoplasty (Daniel, 2002) ; (Flint *et al.*, 2010) . Vessels like an angular artery, col-

umellar artery or smaller capillaries of the subcutaneous plexus on an injury, can contribute to the surgical haemorrhage (Daniel, 2002) which in turn can result in a prolonged surgery leading to post-operative oedema (Tebbetts, 2008). Numerous modalities have been proposed to manage the surgical bleeding during rhinoplasty such as injection of a diluted solution of adrenaline along with the surgical site, raising the level of the head above trunk during the surgery, and hypotensive anaesthesia during surgery (Daniel, 2002) ; (Flint *et al.*, 2010).

Over the past few decades, the strategy of lowering patient's blood pressure during anaesthesia or "Hypotensive anaesthesia" has been practised to reduce the blood loss during surgeries (Bentel, 1968) ; (Warner *et al.*, 1970); (Mostert, 1973); (Ward *et al.*, 1980); (Sataloff *et al.*, 1987). A natural survival mechanism is what lies as a physiological principle behind hypotensive anaesthesia (Sataloff *et al.*, 1987) . Intense bleeding leads to a drop in blood pressure which eventually results in reduced blood loss, stabilisation of blood pressure and recovery (Mostert, 1973) (Ward *et al.*, 1980). Likewise, intentional reduction of blood pressure during surgery can decrease overall intraoperative blood loss (Barak *et al.*, 2015).

Clonidine is an antihypertensive medication with a system of activity that seems to vary from other generally utilised antihypertensive drugs. Administration of astoundingly low doses brings about compelling control of blood pressure in supine and standing positions in moderate or severe hypertension. The useful impacts of clonidine in diminishing the haemorrhage during neurosurgery and orthopaedic surgical procedures, delicate surgical procedures of the ear (Welfringer *et al.*, 1992) , nose (Ilberg *et al.*, 1990) ; (Riegle *et al.*, 1992) and sinus endoscopy have been proved (Kubo *et al.*, 1995) ; (Eberhart *et al.*, 2003).

Mechanism of action of clonidine:

"Clonidine hydrochloride" is an imidazoline compound and an alpha-adrenergic receptor agonist, represented by chemical nomenclature S-(2-6-dichlorphenamide)-2-imidazoline hydrochloride. Clonidine specifically triggers postsynaptic alpha-adrenergic receptors in the depressor site of the vasomotor centre of the medulla oblongata in the locale of the nucleus tractus solitarius (NTS) or locus coeruleus (Kosman, 1975) ; (Pettinger, 1975). Stimulation of these central receptors lessens the efferent sympathetic neuronal vasoconstrictor tone to the heart, kidneys, and peripheral vasculature causing vasodilatation and brings down blood pressure (Schmitt and Schmitt, 1969); (Haeusler *et al.*, 1972) . Clonidine may likewise impact blood pressure through suprabulbar structures such as alpha-adrenergic receptors in the hypothalamus (Kobinger, 1978) . Incitement of peripheral postsynaptic alpha-l vascular smooth receptors may escalate blood pressure (Haeusler, 1974); (Henning, 1974). This might be seen for a very short period after intravenous administration because of direct stimulation (Onesti *et al.*, 1969) or when the chemical compound is given in oral doses beyond the therapeutic range (Davies *et al.*, 1977) . A correlation between plasma drug concentration and the hypotensive effect of clonidine exists only at lower plasma levels. At higher drug concentrations, the noted hypotensive effect is considerably smaller than anticipated as a result of an expanding impact of the pressor component (Kobinger, 1978) . Oral administration of clonidine produces only a hypotensive effect in the initial phase (Onesti *et al.*, 1969) .

Pharmacokinetics of clonidine:

Clonidine is easily assimilated after administration through an oral route with an onset of its antihypertensive activity 30-60 mins following oral administration, and considerable blood pressure devaluation in 1-4 hours (Kosman, 1975) ; (Pettinger, 1975) The most extreme antihypertensive effect, happening at 2-4 hours after an oral dose correlates well with peak plasma levels at 90 mins to 3-5 hours (Cohen and Katz, 1978) . A cosy relationship likewise exists between plasma drug concentration, degree of sedation, decrease in salivary flow and drop in blood pressure (Dollery *et al.*, 1976) ; (Davies *et al.*, 1977) . Plasma clonidine at plasma concentration levels of 1.5-2.0 mg/ml produces sedation and impede salivation (Davies *et al.*, 1977) . Plasma concentrations lower than 2 mg/ml diminishes hypotensive effects, whereas elevated levels of 2-10 mg/ml cause lesser blood pressure decrement than would be expected (Davidov *et al.*, 1967) ; (Onesti *et al.*, 1969) . A dose-dependent decline in blood pressure occurs before these high plasma concentrations are attained (Frisk-Holmberg *et al.*, 1978) . The span of the antihypertensive effect is up to 18 hours. Yet, in certain patients, it might be as short as 4-6 hours or as long as 24-36 hours (Pettinger, 1975) ; (Frisk-Holmberg *et al.*, 1978) . The period of optimal blood pressure control is associated to an extent to the size of the dose. The plasma half-life is generally 12-16 hours (Onesti *et al.*, 1969) ; (Kosman, 1975) . Clonidine is immediately distributed to all tissues and crosses the blood-brain barrier when administered orally or intravenously, with most significant levels being reached in the kidney, liver and spleen (Kosman, 1975) . The drug is

Table 1: Characteristics of the included studies

	(Ghazipour *et al.*, 2013)	(Tabrizi *et al.*, 2014)
Study design	RCT	RCT
Sample size	80	66
Control group	Placebo pill	Placebo pill
Intervention group	Oral clonidine	Oral clonidine
Variables of interest	Intraoperative Blood loss Mean arterial blood pressure Operation time	Intraoperative Blood loss Systolic pressure Diastolic pressure Operation time
Anaesthesia Type	General anaesthesia	General anaesthesia
Mean age	22.5 years	23.24
Gender	Male – 21, Female - 59	Male – 28, Female - 38
Mean duration of surgery	Clonidine – 60 $\pm$ 10 minutes Placebo – 70 $\pm$ 10 minutes	Clonidine – 1.24 $\pm$ 0.48 hours Placebo – 1.21 $\pm$ 0.45 hours
Time of drug administration	60 minutes before procedure	2 hours before procedure
Clonidine dose	5 mcg/kg	0.2 mg (single dose)

RCT – Randomized Control Trials

Table 2: Methodology of the included studies

Author and Year	Outcome	Other Finding	Method of Assessment of Intraoperative Blood loss
(Ghazipour *et al.*, 2013)	Less blood loss with oral clonidine group	No significant difference in blood pressure with both groups	Number of gauzes contaminated with blood
(Tabrizi *et al.*, 2014)	Less blood loss with oral clonidine group	Significant difference was observed in blood pressure with both groups	1.Collection of blood in a surgical suction unit 2.Weight of blood-soaked gauzes (weights were recorded both before and after the surgery)

metabolised primarily in the liver. Faecal elimination ranges from 15% to 30%. Roughly 40% to 60%, of an oral dose, is excreted unaltered in the urine within 24 hours. Total elimination of the drug takes around 120 hours (Kosman, 1975) ; (Dollery *et al.*, 1976)

Adverse effect

Most by far of patients, around ninety-three percentage tolerate the drug adequately. Only seven per cent of patients refrain from clonidine due to intolerable adverse effects. Continued administration of clonidine might cause sedation and dry mouth which are the most typical adverse reactions to the drug, but they tend to be mild and diminish or disappear in 14-28 days (Sung *et al.*, 1971) ; (Igloe, 1973) . But single-dose administration before any surgical procedure to control blood pressure during anaesthesia (adjuvant hypotensive anaesthesia) does not cause any noteworthy adverse effects to the patients. Most of the adverse reactions to clonidine are dose and time related (Mroczek *et al.*, 1975) ; (Pettinger, 1975) . Doses beyond 1.5 mg/day are not usually necessary for controlling blood pressure (Whitsett *et al.*, 1978) . Clonidine is not only used in hypertension but also has been accounted for to have many other clinical uses. These "non-cardiovascular" effects include nasal decongestion, reduced gastric acid production (Onesti *et al.*, 1971) , diminished intestinal motility (Onesti *et al.*, 1969), and local anaesthesia (Kobinger, 1973) . The above mentioned non-cardiovascular effects of clonidine also make it a beneficial agent to use in anaesthesia for providing a better-quality of anaesthesia.

MATERIALS AND METHODS

Structured question

Does premedication with oral clonidine reduce intraoperative blood loss during rhinoplasty

Table 3: Summation of data from the included studies

	(Ghazipour *et al.*, 2013)		(Tabrizi *et al.*, 2014)	
Study Groups	**OCG**	**PG**	**OCG**	**PG**
Age (Mean ± SD)	23 ± 2.1 **(P > 0.05)**	25 ± 3 **(P > 0.05)**	23.24 ± 4.12 **(P > 0.05)**	26.12 ± 6.06 **(P > 0.05)**
Weight (Mean ± SD)	NM		63.33 ± 10.71 **(P > 0.05)**	64.21 ± 10.98 **(P > 0.05)**
Operation Time(Mean ± SD)	62 ± 10 **(P > 0.05)**	70 ± 12 **(P > 0.05)**	1.24 ± 0.48 **(P > 0.05)**	1.21 ± 0.45 **(P > 0.05)**
MAP (Mean ± SD)	88 ±8 **(P > 0.05)**	92 ± 8 **(P > 0.05)**	NM	
IOBL (Mean ± SD)	**(P < 0.05)**	**(P < 0.05)**	68.03 ± 22.49 **(P < 0.05)**	132.12±78.53 **(P < 0.05)**

OCG – Oral Clonidine Group, PG – Placebo Group, SD – Standard Deviation, NM – Not Mentioned, MAP – Mean Arterial Pressure, IOBL – Intra Operative Blood Loss

Table 4: Risk of Bias – Major and Minor Criteria

Author	**(Ghazipour *et al.*, 2013)**	**(Tabrizi *et al.*, 2014)**
Randomization	Yes	Yes
Allocation Concealment	No	No
Assessor Blinding	Yes	No
Dropouts Described	Yes	Yes
Sample Justified	No	No
Baseline Comparison	Yes	Yes
Inclusion / Exclusion Criteria	Yes	Yes
Method Error	No	No
Risk of Bias	Low	Moderate
Level of Evidence	Level 2*	Level 2*

*Based on Oxford Centre for Evidence-based Medicine levels of Evidence (March 2009)

surgery?

Population, Intervention, Comparison and Outcome analysis

Population: Patients undergoing Rhinoplasty surgery

Intervention: Oral Clonidine

Comparison: Placebo

Outcome: Intraoperative blood loss during rhinoplasty surgery

Criteria for inclusion

Randomised and non-randomised controlled clinical trials. In vivo studies and articles published only in the English language were included in this review.

Criteria for exclusion

Animal studies, Retrospective studies, In vitro studies and studies published in languages other than English were excluded from the review process.

Data collection from literature

Data was gathered from electronic databases like PubMed, Medline and Cochrane central library. An additional manual search was performed with various journals to look for available articles to include in the systematic review. Furthermore, the references list of included studies was appraised for additional articles

Search strategy

The search strategy was a list of keywords based on Medical Subject Headings (MeSH) terms with relation to the formulated PICO for this systematic review. The search terms used were rhinoplasty, nasal surgery, bleeding, haemorrhage, blood loss, oral clonidine and imidazoline.

Identification of articles

The review process comprised of two stages. In the preliminary stage, the title and abstracts of the articles retrieved through the electronic (PubMed,

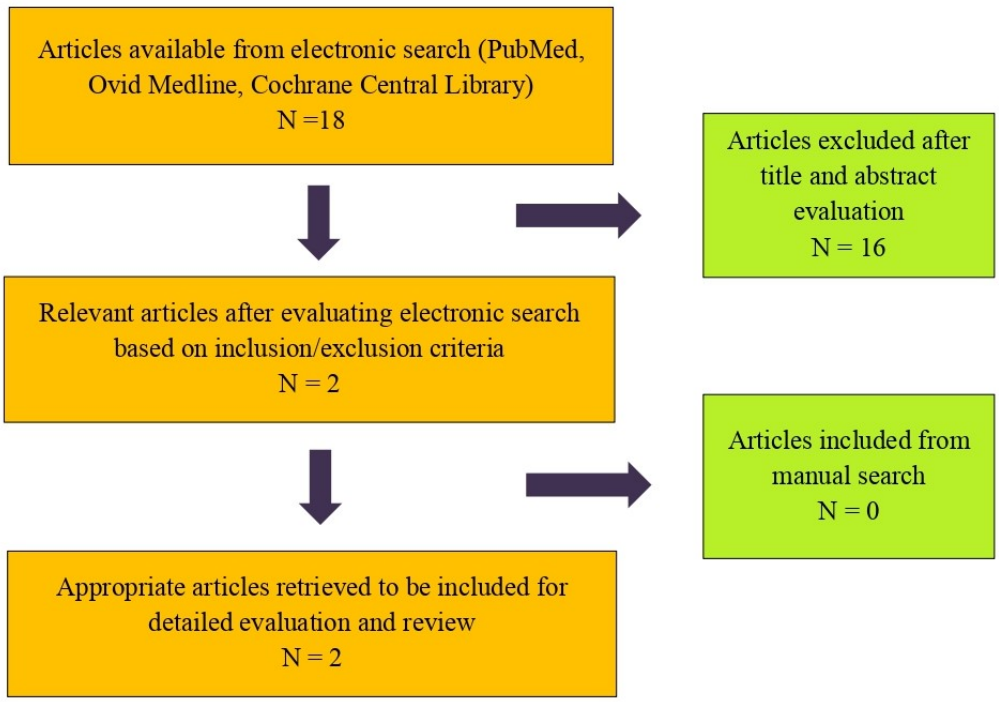

Figure 1: PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart for selection of studies

Cochrane, Medline) search were analysed for pertinence. The full text of pertinent articles was procured and accessed. In the subsequent stage, relevant articles were segregated based on inclusion and exclusion criteria for further data collection. All studies that compared oral clonidine with a control (placebo) in patients requiring rhinoplasty were included for review.

Extraction of data, risk of bias assessment and level of evidence of study

Data extraction for general characteristics and variables of the outcome of all included studies were done. All articles that were determined as suitable for inclusion were read entirely and summarised based on study groups, a total number of samples, study design, method of evaluation, intervention, dosage, outcome and inference.

Intraoperative bleeding and operation time were the variables of interest. All the included studies were subjected to a level of evidence and risk of bias assessment for which consort criteria was used. Out of the four significant categories if a study records three or more ”yes” then the study is of “low risk”, if it records two “yes” then it’s of “moderate risk” and if it records less than two “yes” then the study is regarded as a “high risk” study.

The search through various electronic databases yielded 18 articles based on the search terms. Sixteen studies were avoided as they were insignificant for the review or didn’t meet the criteria for inclusion once their titles and abstracts were read. After the assessment of full texts, the remaining two studies were included for qualitative analysis. The manual search yielded no additional pertinent article for the systematic review. (Figure 1)

RESULTS AND DISCUSSION

Benefits of oral clonidine Premedication in rhinoplasty surgery

Rhinoplasty can be done through various techniques and contradictory approaches which make the surgery a challenging and confusing procedure for most of the surgeons to obtain consistent results (Millard, 1996) ; (Sheen, 2000) . One of the most well-known and inconvenient difficulty during the surgical procedure of rhinoplasty is bleeding. It can impede the vision of the operating surgeon, thereby diminishing the quality of the sur-

gical field. Different strategies have been recommended to decrease the haemorrhage during rhinoplasty surgeries, such as injection of adrenaline along with the surgical site, raising the level of the head above trunk during the operation (Daniel, 2002) ; (Tebbetts, 2008) , and hypotensive anaesthesia to reduce blood pressure during surgery and thereby to reduce the haemorrhage (Flint *et al.*, 2010) .

Clonidine has been utilised for managing immediate post-operative complications like pain, nausea, vomiting and tremor after surgery. It has also been given orally as an adjunct to augment the hypotensive action during the surgery. This drug plays out its antihypertensive effect through abatement of sympathetic outgoing potential (Toivonen and Kaukinen, 1990) . Many studies have proved the use of clonidine as a premedication in reducing the blood loss during various surgeries like middle ear surgery (Welfringer *et al.*, 1992) , neurosurgery, nasal surgeries (Ilberg *et al.*, 1990) ; (Riegle *et al.*, 1992) , endoscopic sinus surgeries and orthopaedic surgeries (Kubo *et al.*, 1995) ; (Eberhart *et al.*, 2003) . Thus, administration of clonidine in oral form as a premedication during surgeries is proved to reduce the intraoperative blood loss during the operation.

So far, there have been two studies that have evaluated the effect of premedication with oral clonidine on reducing the intraoperative bleeding during rhinoplasty surgery (Ghazipour *et al.*, 2013) ; (Tabrizi *et al.*, 2014) . Both the studies have been qualitatively compared and evaluated with tabulation of results in terms of general characteristics, methodology, outcome data, risk of bias and level of evidence. (Tables 1, 2, 3 and 4)

Interpretation of results

According to Tabrizi R. et al. (Tabrizi *et al.*, 2014), reduced blood loss was observed during the surgical procedure of rhinoplasty with Oral clonidine when compared to placebo. Besides, the study also reports a significant reduction in the systolic and diastolic blood pressure with Oral clonidine group. According to Ghazipour A et al. (Ghazipour *et al.*, 2013) , reduced bleeding during the surgical procedure of rhinoplasty with no significant reduction in mean arterial blood pressure was observed with oral clonidine group.

Implication for practice

Clonidine, when administered orally as a premedication before rhinoplasty surgery has proven to reduce the amount of intraoperative blood loss during the surgical procedure. Oral clonidine can be effectively used as an adjunct to hypotensive anaesthesia to augment the effect of hypotension and reduce the bleeding during surgery. Further studies which involve estimation of other parameters like quality of the surgical field, amount of bleeding at a different period during the surgery and operators' comfort are needed to establish this fact furthermore.

Implication for research

Further studies which compare the effect of oral clonidine with other drugs and studies which evaluate the impact of clonidine through different routes of administration will ascertain the best route to reduce the intraoperative bleeding during rhinoplasty surgery. The study of these drugs in terms of economic feasibility should also be evaluated as these drugs may be useful but costly.

CONCLUSIONS

Based on the clinical evidence, administration of oral clonidine as a premedication in patients undergoing rhinoplasty surgery effectively reduces the intraoperative blood loss during the surgical procedure, which may contribute to achieving excellent results. Further studies with larger sample size and studies which evaluate other parameters such as quality of the surgical field and operator satisfaction are necessary to collaborate the findings of the present study for their broader use in clinical practice.

Conflicts of Interest

The authors of the study declare no conflicts of interest for this study.

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