Research Article

Clonidine versus metoprolol in hemorrhage control – A review of literature

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ABSTRACT

Background: One of the major risks during and after surgery is the perioperative blood loss, which significantly contributes to high death rate, post-operative complications, and usage of the health-care resources. **Materials and Methods:** This narrative review was based on a literature search of relevant databases up to December 2019, for publications relevant to reducing blood loss in various surgeries involving the drugs clonidine or metoprolol. **Results:** There are many suggested methods and techniques to reduce blood loss during major surgical procedures which broadly includes organizational, surgical, anesthetic, and hemostatic strategies. Hypotensive anesthesia produces promising results in reducing the intraoperative blood loss by lowering the blood pressure during surgery. Both clonidine and metoprolol potentiate the effect of hypotensive anesthesia and contribute to efficiently controlling the intraoperative hemorrhage. Both clonidine and metoprolol have proved its efficiency in various major surgeries such as spine surgery, gynecologic surgery, neurosurgery, and maxillofacial surgeries. **Conclusion:** Both clonidine and metoprolol show promising results in controlling blood loss during various surgical procedures. Although high-quality evidence exists in certain areas, the overall evidence base for reducing intraoperative blood loss with clonidine and metoprolol remains limited.

KEY WORDS: Blood loss, Clonidine, Hemorrhage, Hypotensive anesthesia, Metoprolol, Transfusion

INTRODUCTION

Around 313 million surgeries are done globally, out of which approximately 4.2 million patients die within 30 days of surgery, accounting for 7.7% of total deaths worldwide, every year.[1,2] One of the major risks during and after surgery is the perioperative blood loss which significantly contributes to the high death rate, post-operative complications, and usage of the health-care resources.[3-5] Blood transfusion is often required to overcome these complications due to blood loss during the surgery. Blood transfusion has the risks of infectious disease incompatibility reactions and immune suppression. In addition, blood transfusion is also proposed to promote tumor growth.[6] Various studies reported the intraoperative blood usage to be either ineffective to improve post-operative outcomes,[7] or found it to be detrimental.[8,9] Advances in anesthesia, surgery, and transfusion medicine over the past decade have led to the development of "patient blood management".[10] It is prudent to try avoiding massive blood losses during major surgeries to prevent subjecting the patient to blood transfusion. There are many suggested methods and techniques to reduce blood loss during major surgical procedures, which broadly include organizational, surgical, anesthetic, and hemostatic strategies.[11] Reducing bleeding with the help of anesthetic strategy includes hypotensive anesthesia technique. Hypotensive anesthesia consists of using pharmacological agents to lower intraoperative mean arterial blood pressure (MAP) to values between 50 and 65 mmHg to reduce blood flow to the surgical field. The intention is to reduce blood loss, while also improving visibility in the surgical field.[12] This review discusses two pharmacological agents, clonidine and metoprolol and their efficacy in reducing the blood loss during major surgical procedures.

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BACKGROUND

Blood loss during various surgeries can be reduced by various pharmacological and non-pharmacological methods.

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Non-pharmacological Methods to Control Blood Loss During Surgery

Non-pharmacological means of minimizing blood loss include good surgical technique, positioning of the surgical field above the level of the heart, acute normovolumic hemodilution, autologous blood donation, and ultrafiltration devices.

Pharmacological Methods to Control Blood Loss During Surgery

Besides hypotensive anesthesia, various drugs used to reduce blood loss during surgeries include desmopressin, tranexamic acid (TXA), hemocoagulase, ε-aminocaproic acid, prostacyclin, dipyridamole, recombinant factor VIIa, aprotinin, and erythropoietin.

Anesthesia Drugs to Control Blood Loss During Surgery

Drugs used in controlled hypotension include the following: [13]

- Primary agents successfully used alone, for example, inhalation anesthetics, sodium nitroprusside, nitroglycerin, trimethaphan, alprostadil (prostaglandin E1), adenosine, remifentanil, and agents for spinal anesthesia
- Agents that can be used alone or as adjuncts to decrease the adverse effects of other agents, for example, calcium channel antagonists (e.g., nicardipine), α-adrenoceptor antagonist (beta-blockers), and fenoldopam
- Secondary agents used only adjunctively with primary agents, for example, angiotensin-converting enzyme inhibitors and clonidine.

CLONIDINE

Clonidine was introduced in 1966.[14] Clonidine was patented in 1961 and came into medical use in 1966. It was first used as a hypertension treatment under the trade name of Catapres.[15] Clonidine hydrochloride is an imidazoline compound, chemical name S-(2-6-dichlorphenylamine)-2-imidazoline hydrochloride. Clonidine acts as an α_2-adrenergic agonist.[16] It is a sympatholytic medication with a history of more than 40 years in clinical use and plays an important role in anesthesia and pain control.[15] Clonidine is an antihypertensive drug with a mechanism of action that appears to differ from other commonly used antihypertensive agents. The administration of remarkably low doses results in highly effective control of blood pressure (BP) in both supine and standing positions in moderate or severe hypertension.

Mechanism of Action of Clonidine

Clonidine is an alpha-adrenergic receptor agonist that selectively stimulates post-synaptic alpha-adrenergic receptors in the depressor site of the vasomotor center of the medulla oblongata in the region of the nucleus of the solitary tract or locus coeruleus. Activation of these central alpha-adrenergic receptors diminishes the efferent sympathetic neuronal vasoconstrictor tone to the heart, kidneys, and peripheral vasculature, causing vasodilation and lowering of BP.[17-22] Although clonidine stimulates the post-synaptic alpha-adrenergic receptor, it actually has both preganglionic and post-ganglionic alpha-adrenergic agonist properties with variable potency in different organs. Clonidine may also influence BP through suprabulbar structures such as alpha-adrenergic receptors in the hypothalamus.[23] Stimulation of peripheral post-synaptic alpha-l vascular smooth receptors may increase BP. This may be seen for a very brief period after intravenous administration due to direct stimulation[24] or when the drug is given in oral doses beyond the therapeutic range.[25] A correlation between plasma drug concentration and the hypotensive effect of clonidine exists only at lower plasma levels. At higher drug concentrations, the observed hypotensive effect is considerably smaller than expected because of an increasing influence of the pressor component.[23] Initial oral administration of clonidine results only in a hypotensive effect.[24]

Pharmacology and Pharmacokinetics

Clonidine is readily absorbed after oral administration with an onset of its antihypertensive action 30–60 min following oral administration, and significant BP reduction in 1–4 h. The maximum antihypertensive effect, occurring at 2–4 h after an oral dose correlates well with peak plasma levels at around 90 min–5 h. A close relationship also exists between plasma drug concentration, degree of sedation, reduction in salivary flow, and fall in BP.[17,18,24-28] Plasma clonidine at plasma concentration levels of 1.5–2.0 μg/ml produces sedation and inhibits salivation.[25] Plasma concentrations of <2 μg/ml reduce hypotensive effects, whereas higher levels of 2–10 μg/ml cause less BP reduction than would be expected. A dose-dependent decrease in BP occurs before these high plasma concentrations are reached.[29] The duration of antihypertensive effect is up to 18 h. However, in some patients, it may be as short as 4–6 h or as long as 24–36 h. The duration of optimal BP control is related in some measure to the size of the dose. The plasma half-life is usually 12–16 h.[17,18,24,29] Clonidine is readily distributed to all tissues and crosses the blood–brain barrier when given orally or intravenously, with the highest levels being reached in the kidney, liver, and spleen.[17] The drug is metabolized mainly in the liver. Fecal excretion ranges from 15% to 30%. Approximately 40–60% of an oral dose is excreted unchanged in the urine within 24 h. Total excretion takes about 5 days.[17,28]

Adverse Effects

The vast majority of patients (93%) tolerated the drug satisfactorily. Only 7% of patients had the need

to discontinue clonidine because of intolerable side effects. The most common side effects, sedation, and dry mouth, are usually mild and tend to decrease or disappear within 2–4 weeks of continued administration. However, single-dose administration before surgery to control BP during anesthesia (adjuvant hypotensive anesthesia) does not cause any significant side effects to the patients. The majority of side effects are dose and time-related.[18,30-32] Doses exceeding 1.2–1.5 mg/day are not commonly necessary to control BP.

Non-cardiovascular Effects of Clonidine

Clonidine has been reported to have many clinical uses other than in hypertension. These "Non-Cardiovascular" effects of clonidine include nasal decongestion, decrease in gastric acid secretion, decrease in intestinal motility, and local anesthesia.[24,33,34] The above-mentioned non-cardiovascular effects of clonidine also make it a beneficial agent to use in anesthesia for providing a better-quality anesthesia.

Efficacy of Clonidine in Reducing Surgical Bleeding

Clonidine is an alpha-2 adrenoceptor agonist that affects sedation and antinociception by stimulating central alpha-2 adrenoceptors at different sites in the central nervous system. Stimulation of medullary alpha-2 adrenoceptors decreases sympathetic tone and increases vagal activity, which blunts the hemodynamic responses to stressful stimuli. In addition, stimulation of presynaptic alpha-2 adrenoceptors decreases the release of norepinephrine at peripheral sympathetic nerve endings, which decreases sympathetic tone.[35] These mechanisms may be responsible for its hypotensive effects, but it has also been shown to potentiate postjunctional alpha-1 adrenoceptor-mediated vasoconstriction.[36-38] The exact mechanism of the potentiation of vasoconstriction by clonidine remains unclear. Although Tanaka and Nishikawa attribute this vasoconstrictive action of clonidine to postjunctional alpha-1 adrenoceptor agonist,[36] Talke *et al.* suggest that clonidine acts on the alpha-2b subtype of alpha-2 adrenoreceptors in peripheral vascular smooth muscle to cause vasoconstriction. Clonidine reduces BP both centrally and peripherally; it increases coagulation due to platelet activation,[39] thus improving surgical field visualization by reducing bleeding.[40] As a central effector, clonidine can reduce post-operative pain, nausea, and vomiting. It also lowers the systemic BP by constriction of peripheral blood vessels, and so decreases the blood flow to the nasal mucosa. Through all these mechanisms premedication with clonidine reduces intraoperative blood loss in various surgical procedures. Clonidine premedication has been successfully used to control BP, tachycardia, vomiting, and bleeding, as well as for post-operative analgesia in many fields of surgery.[16,41-47]

Efficacy of Clonidine in Functional Endoscopic Sinus Surgery (FESS)

Surgical bleeding during FESS decreases the visibility of the surgical field during an intervention, increases the incidence of serious vascular, orbital, and intracranial complications, prolongs surgical duration, and reduces the quality of intervention. Various methods, such as pre-operative adrenaline packing of the nasal cavity, intraoperative adrenaline infiltration of the nasal mucosa, patient head elevation, and/or hypotensive anesthesia, have been adopted to provide an optimal field. Many recent studies on the effect of clonidine in FESS concluded that clonidine reduces arterial BP and increases surgeon visualization during surgery. Premedication with oral clonidine provides a more vivid view of the surgical field, decreasing blood loss while significantly increasing the surgeon's satisfaction when FESS is performed due to nasal polyposis. In addition, they have reported shorter surgical time and reduced bleeding.[48] A better surgical field and lower morbidity of patients undergoing FESS were reported in the clonidine group.[42] Comparative evaluation of oral premedication of clonidine with metoprolol and midazolam resulted in the former drug being more effective.[47,49,50]

The surgical conditions following premedication with oral clonidine versus oral diazepam for endoscopic sinus surgery concluded that premedication with clonidine as compared to diazepam, provides a better surgical field with less blood loss in patients undergoing ESS.[51] Premedication with oral clonidine and intravenous TXA has the same effect on bleeding during FESS, surgical field visualization, and surgeon satisfaction with no difference in post-surgical hemoglobin level, BP, and heart rate.[52]

Efficacy of Clonidine in Rhinoplasty Surgeries

During the past decade there was a great tendency towards cosmetic surgery, especially rhinoplasty surgery. One of the most common and troublesome complications during rhinoplasty surgery is bleeding.[53,54] Hemorrhage during the surgery may occur as a result of the damage to each great vessel, such as an angular artery or small vessels (capillaries) in the subcutaneous plexus. Induced hypotension during surgery produces promising results in reducing the bleeding during the procedure. Premedication with oral clonidine significantly reduced intraoperative blood loss in rhinoplasty surgeries when compared with a placebo.[55,56]

Efficacy of Clonidine in Spine Surgery

Spinal fusion surgery is often associated with major blood loss, which is sometimes significant, requiring the transfusion of blood or blood products.[57] Decreasing bleeding is important to maintain a patient's hemodynamic stability and improves the surgical

field. In spine surgery, the latter aspect is especially important, due to the vicinity of major and highly fragile neurological structures. The surgeon's comfort shortens the operating time, which further decreases bleeding.[58] Oral premedication with clonidine can reduce surgical blood loss in lumbar spine posterior fusion surgery, even at the same levels of mean arterial pressure when compared with propofol and remifentanil.[59] Premedication with clonidine decreases intraoperative blood loss and can be more effective in patients with opium addiction than the ones without addiction.[60]

Efficacy of Clonidine in Otolaryngologic Surgery

Middle ear and nasal surgery are a delicate and time-consuming procedure requiring a bloodless surgical field. Premedication with clonidine reduced bleeding in middle ear microsurgery, attenuated hyperdynamic response to tracheal intubation, and reduced isoflurane, fentanyl, and urapidil requirements for controlled hypotension.[44] Premedication with intravenous (IV) clonidine in a dose of 4 and 5 μg/kg reduces bleeding and provides a clear field for surgery. It also reduces the requirement of isoflurane, fentanyl, and metoprolol for controlled hypotension. However, clonidine 5 μg/kg is not more effective than clonidine 4 μg/kg in producing these effects rather it was associated with some side effects.[61]

Efficacy of Clonidine in Neurosurgery

Pituitary masses are common lesions accounting for about 15–20% of all brain tumors. Oozing blood is an annoyance in microscopic sublabial trans-sphenoidal approach for these masses. There have been many ways of reducing the ooze, having their own pros and cons. Clonidine is a safe and effective drug to reduce bleeding in trans-sphenoidal microscopic pituitary adenoma surgery which can provide less blood loss during surgery, better operative field, and reduces operation time.[62]

Efficacy of Clonidine in Orthognathic Surgery

Jaw skeletal discrepancy is an acquired or congenital deformity which requires single or double-jaw orthognathic surgery. A surgical site with the least bloodshed possible contributes to decreased surgical time, better visualization of the surgical field, and increased quality of the surgery. Induced hypotension is a way to achieve this goal in orthognathic surgery and is currently reaching increased popularity. Control of BP for the first time in the operating room with this method was performed in 1946.[63] In orofacial corrective surgery, hypotensive anesthesia was applied in 1976.[64] A 300 μg quantity of clonidine, administered 90 min before surgery as an oral premedication, is a practical, easy, and inexpensive method with the least possible complications. It may cause decreased blood loss and surgery time and improves the field of view during surgery, increasing surgeon satisfaction during bimaxillary orthognathic surgery.[40]

Use of Clonidine in Dentoalveolar Surgery

In dental practice, clonidine is also used for other uses such as pain management, anxiety management and modulating the effect of local anesthesia. Adrenaline at 10 μg/ml and clonidine at 15 μg/ml can be safely used as additives with lignocaine in maxillary infiltration anesthesia for dental extraction; with the addition of either of these two drugs, having an equal advantage over the use of plain lignocaine; in terms of lower blood loss and longer duration of anesthesia; but, with no difference in the onset of anesthesia and with no significant hemodynamic changes.[65] Similar other studies also concluded that clonidine was as effective as adrenaline with lignocaine,[66] clonidine was better with hemodynamic parameters,[67] and clonidine showed better post-analgesic effect in patients than epinephrine.[68]

METOPROLOL

Metoprolol was first discovered in 1969 by Ablad and Carlsson. Metoprolol was the first clinically used cardioselective β-blocker. Metoprolol has affinity for β1-receptors, 30 times more than its affinity for β2-receptors. As with any cardioselective β-blocker, higher serum levels may result in greater incidence of β2-blocking effects. Metoprolol is administered intravenously in 1–2 mg doses, titrated to effect. The potency of metoprolol is approximately one-half that of propranolol. Maximal β-blocker effect is achieved with 0.2 mg/kg given intravenously.[69] Metoprolol is a beta1-selective adrenoceptor blocking drug. In hypertension, its duration of effect is longer than expected from its half-life and it is suitable for twice daily administration. There is some evidence that once daily administration may be possible in treating hypertension. It is similar in efficacy to other beta-adrenoceptor blocking drugs in angina pectoris and essential hypertension when given in equally active beta-blocking dosages. Metoprolol is well tolerated and side effects have not proved a problem. It has some pharmacodynamic and pharmacokinetic differences from other beta-adrenoceptor blocking drugs and may prove useful in cases where these differences are shown to be clinically important.[70]

Chemistry

Metoprolol has a very low melting point; around 120°C (248°F) for the tartrate, and around 136°C (277°F) for the succinate. Because of this, metoprolol is always manufactured in a salt-based solution, as drugs with low melting points are difficult to work within a manufacturing environment. The free base exists as a waxy white solid, and the tartrate salt is finer crystalline material.

The active substance metoprolol is employed either as metoprolol succinate or metoprolol tartrate (where 100 mg metoprolol tartrate corresponds to 95 mg metoprolol succinate). The tartrate is an immediate-release formulation, and succinate is an extended-release formulation.[69]

Pharmacology

General pharmacological principles of metoprolol:

- Beta-1 selective
- Moderately lipophilic
- Without intrinsic sympathomimetic activity
- With weak membrane stabilizing activity
- Decreases heart rate, contractility, and cardiac output, therefore decreasing BP.

Mechanism of Action

Metoprolol blocks β1 adrenergic receptors in heart muscle cells, thereby decreasing the slope of phase 4 in the nodal action potential (reducing Na^+ uptake) and prolonging repolarization of phase 3 (slowing down K^+ release). It also suppresses the norepinephrine-induced increase in the sarcoplasmic reticulum (SR) Ca^{2+} leak and the spontaneous SR Ca^{2+} release, which is the major trigger for atrial fibrillation.[70]

Pharmacokinetics

Metoprolol has a short half-life of 3–7 h, so is taken at least twice daily or as a slow-release preparation. It undergoes α-hydroxylation and O-demethylation as a substrate of the cytochrome liver enzymes CYP2D6 and a small percentage by CYP3A4, resulting in inactive metabolites.[70]

Overdose

Excessive doses of metoprolol can cause severe hypotension, bradycardia, metabolic acidosis, seizures, and cardiorespiratory arrest. Blood or plasma concentrations may be measured to confirm a diagnosis of overdose or poisoning in hospitalized patients or to assist in a medicolegal death investigation. Plasma levels are usually <200 μg/l during therapeutic administration, but can range from 1 to 20 mg/l in overdose victims.[70]

Adverse Effects

Adverse effects, especially with higher doses, include dizziness, drowsiness, fatigue, diarrhea, unusual dreams, trouble sleeping, depression, and vision problems. β-blockers, including metoprolol, reduce salivary flow through inhibition of the direct sympathetic innervation of the salivary glands. Metoprolol may also reduce blood flow to the hands or feet, causing them to feel numb and cold; smoking may worsen this effect. Due to the high penetration across the blood–brain barrier, lipophilic beta-blockers such as propranolol and metoprolol are more likely than other less lipophilic beta-blockers to cause sleep disturbances such as insomnia, vivid dreams, and nightmares.[69] Serious side effects that are advised to be reported immediately include symptoms of bradycardia (resting heart rate slower than 60 beats/min), persistent symptoms of dizziness, fainting and unusual fatigue, bluish discoloration of the fingers and toes, numbness/tingling/swelling of the hands or feet, sexual dysfunction, erectile dysfunction, hair loss, mental/mood changes, depression, breathing difficulty, cough, dyslipidemia, and increased thirst. Consuming alcohol while taking metoprolol may cause mild body rashes and is not advised.[70]

Precautions

As with other α-adrenoceptor blocking drugs, patients with mild or latent cardiac insufficiency should be given a diuretic and/or adequate doses of digitalis before receiving metoprolol. Metoprolol may be administered with caution to patients with bronchitis and a tendency to wheezing, provided that bronchodilator therapy with a α_2 adrenoceptor stimulant drug such as terbutaline and salbutamol is administered concomitantly. Although it is best to avoid any α-adrenoceptor blocking drug in asthma, some consider that low doses of metoprolol (up to 100 mg daily) may be given if it is thought essential in asthmatic patients, who must also be receiving optimum regular therapy with α_2 adrenoceptor stimulants.[69] It may be necessary to increase the dose of α_2-stimulant or institute combined oral and inhalation therapy in these patients. Metoprolol therapy must be reported to the anesthetist before general anesthesia for surgery. Caution should be observed when treating patients with unstable diabetes mellitus, as adjustment of the dose of the hypoglycemic agent may be necessary. Pending further clinical experience, metoprolol is not recommended for use during pregnancy.[70]

Efficacy of Metoprolol in Reducing Surgical Bleeding by Controlled Hypotension

Metoprolol has been used as an adjunct to sodium nitroprusside for reducing tachycardia and helping to decrease BP during surgical procedures requiring controlled hypotension.[71,72] Metoprolol proved to be a useful adjunct to the induced hypotension in maintaining heart rate intraoperatively.[71] Metoprolol 0.69 μg/kg/min given by continuous intravenous administration is a useful adjunct to sodium nitroprusside for inducing controlled hypotension in patients undergoing neurosurgical operations for cerebral aneurysm. This combination is more effective than sodium nitroprusside alone for avoiding reflex tachycardia and postsurgical hypertension. By effectively reducing the BP, premedication with metoprolol is proven to reduce intraoperative blood loss in various surgeries.[72]

Efficacy of Metoprolol in Nasal and Functional Endoscopic Sinus Surgeries

Metoprolol significantly improves visual clarity and hemodynamics during FESS.[73] Decrease in both systolic BP and heart rate to <60 beats/min reduces intraoperative bleeding. These rates can be achieved using metoprolol. Using a double-dose of metoprolol significantly reduces intraoperative bleeding and improves the quality of the operative field. It also reduces patients' agitation in the recovery room.[74]

Efficacy of Metoprolol in Orthognathic Surgery

Orthognathic surgery may often require blood transfusion. To correct this complication, controlled hypotension during a surgical procedure decreases BP and subsequently improves the surgical field.[75-77] Premedication with both oral telmisartan 40 mg and metoprolol 100 mg along with fentanyl and sevoflurane anesthesia decreases blood loss. There is also an achievement of satisfactory deliberate hypotension during orthognathic surgery with both the drugs. The outcome of anesthesia is better with telmisartan and metoprolol such as reduced surgery duration, reduced duration of blood loss, and reduced additional use of drugs.[78]

Efficacy of Metoprolol in Gynecologic Surgery

Hysterectomy is one of the most common surgeries performed in India. Hysterectomy is associated with significant morbidity, including blood loss. Several studies have investigated different interventions that share the potential to (directly or indirectly) diminish or stop blood flow to the uterus to permit safe completion of a hysterectomy with a minimum blood loss. Oral premedication with metoprolol attenuates the hypertensive response to tracheal intubation and reduces both arrhythmias and operative blood loss in patients undergoing elective hysterectomy.[79]

Comparison of Clonidine and Metoprolol

Although various studies have evaluated the effectiveness of clonidine and metoprolol on controlling blood loss during various surgeries, there have not been adequate clinical trials that comparatively evaluated the effect of clonidine and metoprolol in reducing the intraoperative bleeding. Puthenveettil *et al*. reported that clonidine was superior to metoprolol in decreasing the amount of blood loss during functional endoscopic sinus surgeries.[49] Many such clinical trials that evaluate the efficacy of both these agents in various major surgical procedures are required to arrive at conclusive evidence of which is the best drug in effectively managing intraoperative hemorrhage.

CONCLUSION

The potential for major intraoperative blood loss remains a key concern for surgeons and anesthetists. During surgery, meticulous surgical techniques, and local hemostasis are fundamental measures in the control of bleeding. Hypotensive anesthesia produces promising results in reducing the intraoperative blood loss by lowering the BP during surgery. Both clonidine and metoprolol potentiate the effect of hypotensive anesthesia and contributes in efficiently controlling the intraoperative hemorrhage. Usage of these agents appropriately during surgeries can be beneficial both to the patient and the surgeon by proving economically effective and positively reinforcing the surgical outcome.

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