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Original Article / Özgün Araştırma

Comparison of Metoprolol and Tramadol with Remifentanil in Endoscopic Sinus Surgery: A Randomised Controlled Trial

Endoskopik Sinüs Cerrahisinde Metoprolol ve Tramadolün Remifentanil ile Karşılaştırılması: Randomize Kontrollü Çalışma

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Abstract / Öz

Objective: Controlled hypotension is commonly induced during functional endoscopic sinus surgery to limit mucosal bleeding. This may be detrimental to elderly patients and patients with arterial stenosis. The aim of this pilot study was to determine if a normotensive anaesthetic technique with sufficient analgesia and without profound vasodilation may reduce intraoperative bleeding and incidence of adverse haemodynamic effects associated with vasodilation and variable rate continuous infusions.

Methods: In this double-blind randomised controlled trial in a tertiary care centre, a total of 88 patients were randomised to receive intravenously either 0.1 mg kg^{-1} metoprolol and 1 mg kg^{-1} tramadol following anaesthesia induction (MT group) or a bolus dose of 0.5 μg kg^{-1} remifentanil following anaesthesia induction, followed by 0.25-0.5 μg kg^{-1} min^{-1} remifentanil infusion (R group). The primary outcome was quality of surgical field and incidence of adverse haemodynamic effects. The secondary outcomes were time to achieve intraoperative bleeding score <3, bleeding rate and changes in cerebral regional oximetry.

Results: A total of 105 patients were recruited, in which 88 were randomised. The median intraoperative bleeding score was similar (1, interquartile range: 1-1, p=0.69). The mean bleeding rate was lower in the MT group, although the difference was not significant (p=0.052, 95% CI 0 to 8.8). Hypotension, bradycardia and cerebral desaturation in the MT group were not observed compared to hypotension in 3 (7%), bradycardia in 18 (41%) and cerebral desaturation in 2 (5%) patients in the R group (p=0.241, p<0.001, p=0.474, respectively).

Conclusion: Providing sufficient analgesia and eliminating stress response can provide stable heart rate and good surgical field with no need for additional hypotension. This normotensive technique may be useful in patients with stenotic arteries or ischaemic organ diseases.

Keywords: Sinus surgery, quality of surgical field, haemodynamic effect, adverse event, bleeding

Amaç: Fonksiyonel endoskopik sinüs cerrahisinde mukozal kanamayı sınırlandırmak amacıyla sıklıkla kontrollü hipotansiyon uygulanır. Bu hipotansiyon yaşlı hastalar ve arteriyel stenozu olan hastalarda zararlı olabilir. Bu pilot çalışmada, yeterli analjeziyle desteklenen, belirgin vazodilatasyon yaratmayan, normotansif bir anestezi tekniğinin intraoperatif kanamayı azaltmadaki etkinliğinin ve vazodilatasyonla ve değişken hızlı sürekli infüzyonla ilişkili hemodinamik yan etkileri araştırılması amaçlandı.

Yöntemler: Üçüncü basamak hastanede yapılan bu çift kör randomize kontrollü çalışmada, 88 hasta iki gruba randomize edildi: Gruplara intravenöz yoldan ya anestezi indüksiyonu sonrası 0,1 mg kg^{-1} metoprolol ve 1 mg kg^{-1} tramadol uygulandı (Grup MT); ya da anestezi indüksiyonu sonrası 0,5 μg kg^{-1} remifentanil bolus dozu ve devamında 0,25-0,5 μg kg^{-1} $dakika^{-1}$ remifentanil infüzyonu uygulandı (Grup R). Primer sonuçlar cerrahi sahanın kalitesi, ve cerrahi süresince hemodinamik yan etkilerin sıklığıydı. Sekonder sonuçlar intraoperatif kanama skorunun 3'ün altına düşmesi için gereken süre, kanama hızı, serebral rejyonel oksimetride değişikliklerdi.

Bulgular: Çalışmaya alınan 105 hastadan 88'i randomize edildi. Medyan intraoperatif kanama skoru her iki grupta benzerdi (1, çeyrekler açıklığı 1-1, p=0,69). Ortalama kanama hızı Grup MT'de daha düşüktü fakat fark istatistiksel olarak anlamlı değildi (p=0,052, %95 güven aralığı 0-8,8). Grup MT'de hipotansiyon, bradikardi, serebral desatürasyon gözlenmezken, Grup R'de 3 hastada hipotansiyon (%7), 18 hastada bradikardi (%41), 2 hastada serebral desatürasyon (%5) gözlendi (sırasıyla p=0,241, p<0,001, p=0,474).

Sonuç: Yeterli analjezi ve stres yanıtının baskılanması, ek hipotansiyon gerekmeden stabil kalp hızı ve kansız bir cerrahi saha sağlayabilir. Bu normotansif anestezi tekniği, stenotik arterlere veya iskemik organ hastalıklarına sahip hastalarda yararlı olabilir.

Anahtar Kelimeler: Sinüs cerrahisi, cerrahi saha kalitesi, hemodinamik etki, yan etki, kanama

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Introduction

Functional endoscopic sinus surgery (FESS) is an established treatment for chronic rhinosinusitis and polyposis resistant to other medical treatments (1). Mucosal bleeding during FESS severely distorts the endoscopic field, prolonging surgery and predisposing the patient to severe complications (2). To limit this bleeding, anaesthesiologists commonly induce controlled hypotension intraoperatively (3).

The techniques initially used for achieving hypotension, such as increasing the end-tidal concentration of inhaled anaesthesia or applying high amounts of opioids, commonly caused delayed awakening. This undesirable complication fuelled research for alternative methods. One such alternative involved employing intermediate-acting beta blockers, such as metoprolol, which are used to reduce the stress response induced by surgery and to provide haemodynamic stability (4).

Remifentanil is an opioid, reaching its peak effect quickly after a bolus dose. It provides easily titratable analgesia, bradycardia and vasodilation (5). Moreover, it is rapidly eliminated by non-specific esterases, allowing its effect to diminish within 5 to 10 min after discontinuing its administration. Owing to these characteristics, it has become the preferred drug for use in controlled hypotension when combined with any amnesic drug.

The same characteristics, however, mean that the use of remifentanil requires very close monitoring, as bolus doses and sudden discontinuations can produce marked adverse haemodynamic effects. Moreover, the analgesic effects of remifentanil do not extend to the immediate postoperative period (6) when patients often experience discomfort due to sutures or nasal packs. This necessitates the use of additional analgesia (7). These reasons led researchers to attempt to identify a better drug to use for controlled hypotension (8).

This pilot study hypothesised that providing sufficient analgesia and attenuating surgery-induced stress response without profound vasodilation may reduce intraoperative bleeding, as well as the incidence of adverse haemodynamic effects associated with vasodilation and variable rate continuous infusions. This is a normotensive anaesthetic technique to control bleeding that permits only as much vasodilation as the main anaesthetic drug causes and can have great benefits for elderly patients and patients with arterial stenosis (9).

A randomised prospective study was designed to test this hypothesis. It aimed to compare remifentanil-induced controlled hypotension with a normotensive anaesthetic technique involving a combination of metoprolol and tramadol in patients undergoing FESS. Intravenous (IV) tramadol was selected to compensate for the lack of analgesic properties of metoprolol, as it is an opioid with local anaesthetic properties that has been effectively used in septal surgeries (10, 11).

Methods

Patients

The Recep Tayyip Erdogan University Ethics Committee (no.: 2015/14, ClinicalTrials.gov ID: NCT02484859) approved the study. Patients with chronic rhinosinusitis or polyposis who were scheduled for FESS between July 2015 and July 2016 were recruited. Patients who were <18 years or >65 years, were alpha-blockers and who had undertreated hypertensive disease, asthma, haemoglobin A1c level >7.5%, concurrent surgery, active pregnancy, an American Society of Anesthesiologists (ASA) physical status >2, history of drug abuse, history of postoperative nausea and vomiting (PONV) or history of allergy to any of the study drugs. Informed consent was obtained from the patients. During the preoperative examination, a sealed-envelope technique was used to randomise patients into two groups: MT group who received a combination of metoprolol and tramadol and R group who received an infusion of remifentanil after anaesthesia induction.

Monitoring and induction of anaesthesia

Following premedication with 0.02 mg kg^{-1} IV midazolam, participants underwent electrocardiography, pulse oximetry, non-invasive blood pressure measurement, bispectral index (BIS) analysis (BIS Vista Monitoring System; Covidien-Medtronic, MN, USA) and regional cerebral oximetry (rSO_2) (INVOS 5100C; Covidien-Medtronic, MN, USA). All patients received 7 mL kg^{-1} isotonic IV fluid within the first 30 min of surgery, and anaesthesia was induced with 2 mg kg^{-1} IV propofol and 2 μg kg^{-1} IV fentanyl. A neuromuscular block was provided with 0.6 mg kg^{-1} IV rocuronium and monitored using a neuromuscular monitor (Datex-Ohmeda M-NMT module; Datex-Ohmeda, Madison, WI, USA). Additional bolus doses were administered to maintain a train-of-four (TOF) count of 1-2.

Anaesthesia was maintained with 60% N_2O, 40% O_2 and 4% desflurane in 0.5-1 L min^{-1} fresh gas flow. All patients received a tidal volume of 7 mL kg^{-1} with 5 cm H_2O positive end-expiratory pressure, and the frequency was titrated to maintain end-tidal carbon dioxide pressure at 37-42 mmHg. The fraction of inspired oxygen was titrated to maintain peripheral oxygen saturation >95% and rSO_2 >75% of the individual baseline value. Desflurane concentration was titrated to maintain a BIS value at 40%-60%, with no burst suppression pattern to prevent overdosing on inhaled anaesthesia.

After surgery, when the TOF ratio increased to >25%, all patients received 15 μg kg^{-1} IV atropine, followed by 50 μg kg^{-1} IV neostigmine for reversal of neuromuscular block. Patients were extubated when the BIS value was >80% with a TOF count of 4 at the adductor pollicis.

Study protocol

Figure 1 shows a schematic diagram of the study protocol. The MT group received a bolus dose of 0.1 mg kg^{-1} IV metoprolol within 1 min of anaesthesia induction and 1 mg kg^{-1} IV tramadol in 100 mL isotonic fluid within 30 min. The R group received an

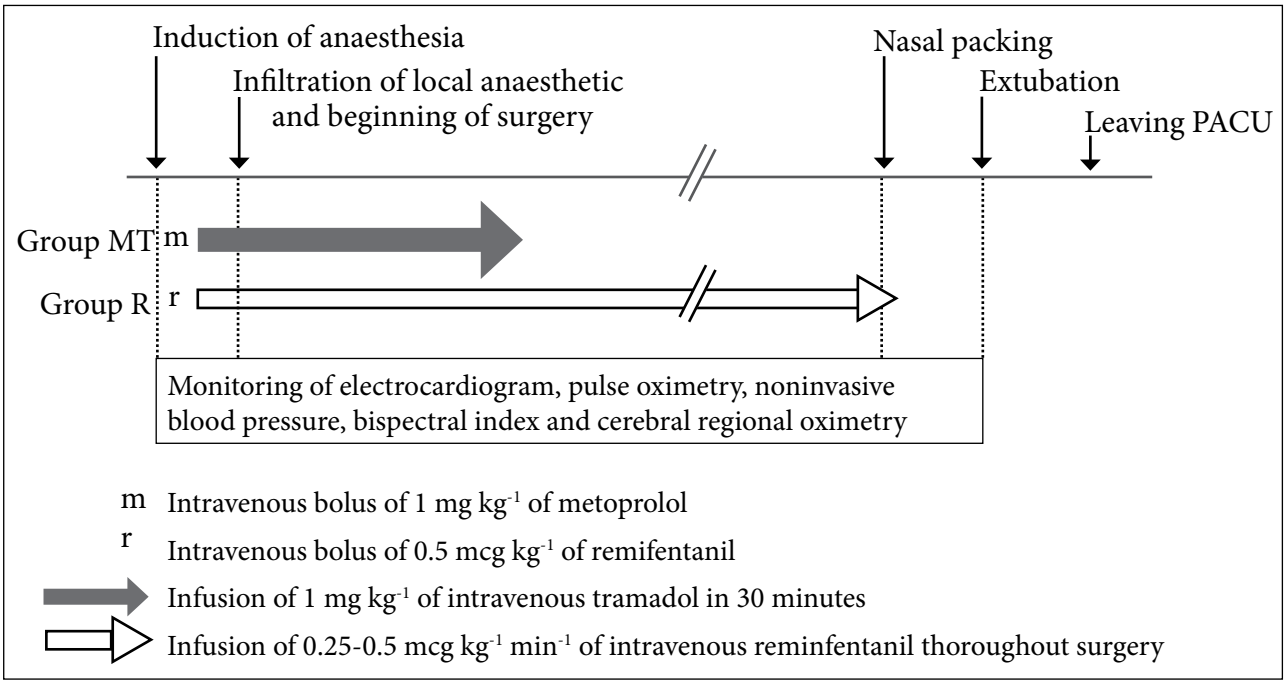

Figure 1. Diagram of the study protocol

Table 1. Intraoperative bleeding score as described by the Boezaart scale

Score	Definition
0	No bleeding
1	Slight bleeding, no suctioning of blood required
2	Slight bleeding, occasional suctioning required. Surgical field not threatened
3	Slight bleeding, frequent suctioning required. Bleeding threatens surgical field a few seconds after suction is removed
4	Moderate bleeding, frequent suctioning required. Bleeding threatens surgical field directly after suction is removed
5	Severe bleeding, constant suctioning required. Bleeding rate is faster than its removal by suctioning as surgical field is severely threatened, and surgery becomes impossible

IV bolus of 0.5 μg kg^{-1} remifentanil within 1 min of anaesthesia induction, followed by an IV infusion at a rate of 0.25-0.5 μg kg^{-1} min^{-1}. Remifentanil infusion was titrated to achieve a mean blood pressure 20%-30% lower than the baseline value.

In the present study, hypotension was defined as having a mean arterial blood pressure <30% of the baseline value, and bradycardia was defined as having a heart rate <50 beats min^{-1}. Both were treated by temporarily reducing the end-tidal concentration of desflurane in the MT group and by decreasing the infusion rate of remifentanil or stopping it, if necessary, in the R group. In case of persistent hypotension or bradycardia, patients received 5 mg IV ephedrine or 0.5 mg IV atropine, respectively.

In the MT group, hypertension and tachycardia were not treated unless the BIS value increased to >60%. In such cases, the end-tidal concentration of desflurane was increased until the BIS value decreased to <60%. In the R group, hypertension (mean arterial blood pressure >80% of the baseline value) and tachycardia (heart rate >80 beats min^{-1}) were treated by increasing the rate of remifentanil infusion. All dose adjustments and adverse haemodynamic events necessitating treatment were recorded.

Data from the cerebral oximeter were analysed. A decrease of <75% of the baseline value was recorded as a cerebral desaturation. The mean and minimum values of rSO_2 and the area under the curve for rSO_2 values <75% of the baseline (AUC_{rSO2} <75%) were also analysed. When the baseline rSO_2 was <50%, the rSO_2 values <80% were considered instead.

Surgical management

All patients underwent intraoperative image guidance and infiltration of the nasal mucosa with 2% lidocaine combined with 5 μg mL^{-1} epinephrine. The two surgeons who participated in the study were blinded to the anaesthetic regimen through the use of a perfusor for the administration of tramadol and remifentanil. Intraoperative bleeding was classified according to a six-point Boezaart scale by the surgeon (Table 1) who was allowed to report the bleeding score at any time point during surgery. This scale is commonly used in the literature for operative field conditions (12). Nasal packing was applied for all patients in the middle meatus at the end of the surgical procedure.

Postoperative measurements

After each surgery, the bleeding rate was calculated (mL min^{-1}) by dividing the total amount of bleeding (amount of blood

in the graded suction container and sponges minus the total amount of irrigation fluid) by surgery duration (excluding the time taken for local anaesthetic infiltration and nasal packing). Blood pressure and heart rate values were recorded every 3 min in the operating room and the post-anaesthetic care unit (PACU). On patient request, postoperative pain was treated with 1 g IV paracetamol, and PONV was treated with 10 mg IV metoclopramide. Upon patient arrival at the PACU and at discharge, the analgesic requests, degree of postoperative pain (Visual Analogue Scale (VAS) ranging from 0: no pain to 10: worst pain) and PONV (four-point ordinal scale with 0: none, 1: nausea, 2: retching and 3: vomiting) were recorded by an anaesthesia technician blinded to the drugs used.

Endpoints

The primary outcome measures were the median intraoperative bleeding score and the incidence of adverse haemodynamic effects throughout surgery. The secondary outcome measures included the time required to achieve an intraoperative bleeding score <3, bleeding rate, changes in the cerebral regional oximetry, degree of postoperative pain and incidence of PONV in the PACU.

Statistical analysis

Statistical analyses were performed using the R statistical program version 3.3.0 (R Foundation, Vienna, Austria). A sample size of 44 patients in each group was sufficient to detect a difference of 0.2 in the mean (standard deviation of 0.4) with an 80% power with an alpha error of 0.05 and a beta error of 20% in this pilot study. The Shapiro-Wilk test was used for normal distribution of data. Data were expressed as mean±standard deviation and analysed using the Student's t-test.

The Wilcoxon test or chi-square test analysed patient demographics. Since surgical duration was different for each patient, a common time base was built by dividing each intraoperative period into 60 equal parts (using movavg function from igraph R package version 1.0.1), similar to the method employed by Nathan et al. (13). Hence, each patient had 60 measurements to analyse. This type of time series data (intraoperative bleeding score, mean arterial blood pressure and heart rate) was compared to repeated measures analysis of variance. In addition, data at individual time points (induction of anaesthesia, intubation and extubation of the trachea and beginning and end of surgery) were compared to Student's t-test.

Medians (interquartile range, IQR) were used and analysed using the Wilcoxon test for non-parametric data. Categorical variables (incidence of cerebral desaturation, hypotension and bradycardia; VAS and PONV scores and number of analgesic requests) were expressed as percentages and compared using the chi-square test. A p value <0.05 was considered statistically significant.

Results

Patients

Data obtained from 88 patients were analysed. The consort flow diagram and patient demographics are presented in Figure 2 and Table 2, respectively. The duration of surgery and anaesthesia was similar in both groups, as well as the number of opened sinuses (Table 3).

Intraoperative bleeding

The median intraoperative bleeding score for both groups was 1 (IQR: 1-1, range: 1-3, p>0.05). Figure 3 shows the variations in bleeding score. The mean time required to achieve an intraoperative bleeding score of <3 in the MT group (13.4±4.2 min) was significantly longer than that in the R group (8.3±2.1 min, p<0.001). Patients in the MT group also had a lower bleeding rate, but the difference was not statistically or clinically significant (27±9 vs. 32±12 mL h^{-1}, p=0.052).

Haemodynamic parameters

Variations in mean arterial blood pressure and heart rate are shown in Figures 4 and 5, respectively. Briefly, blood pressure was lower in the R group throughout the surgical period (Table 3). However, there was no difference after intubation of the trachea and at the arrival to the PACU.

Haemodynamic adverse effects

No adverse haemodynamic events necessitating treatment were observed in the MT group (Table 3). Hypotension occurred in 3 (7%) patients who were treated by discontinuing remifentanil infusion and administering 5 mg ephedrine in the R group. The rate of remifentanil infusion in the R group was frequently adjusted due to bradycardia (2±0.8 dose adjustments h^{-1}), which was not observed in the MT group (Table 3).

Cerebral desaturation

Two (5%) patients in the R group had cerebral desaturation compared to none in the MT group (Table 3).

Immediate postoperative pain and nausea

The degree of postoperative pain and the incidences of PONV in the PACU were similar in both groups (Table 4).

Discussion

This pilot study demonstrated that single doses of IV metoprolol and tramadol may provide a level of surgical vision comparable to that provided by continuous remifentanil infusion while ensuring a lower incidence of adverse haemodynamic effects. While the median intraoperative bleeding score was similar for both groups, no significant haemodynamic fluctuation was observed in the MT group, and there were no cases where the expired desflurane concentration had to be increased. In contrast, patients in the R group required frequent remifentanil dose changes. Moreover, in three cases, remifentanil infusion had to be temporarily stopped due to hypotension. Bradycardia was also very common with remifentanil, necessitating frequent dose adjustments.

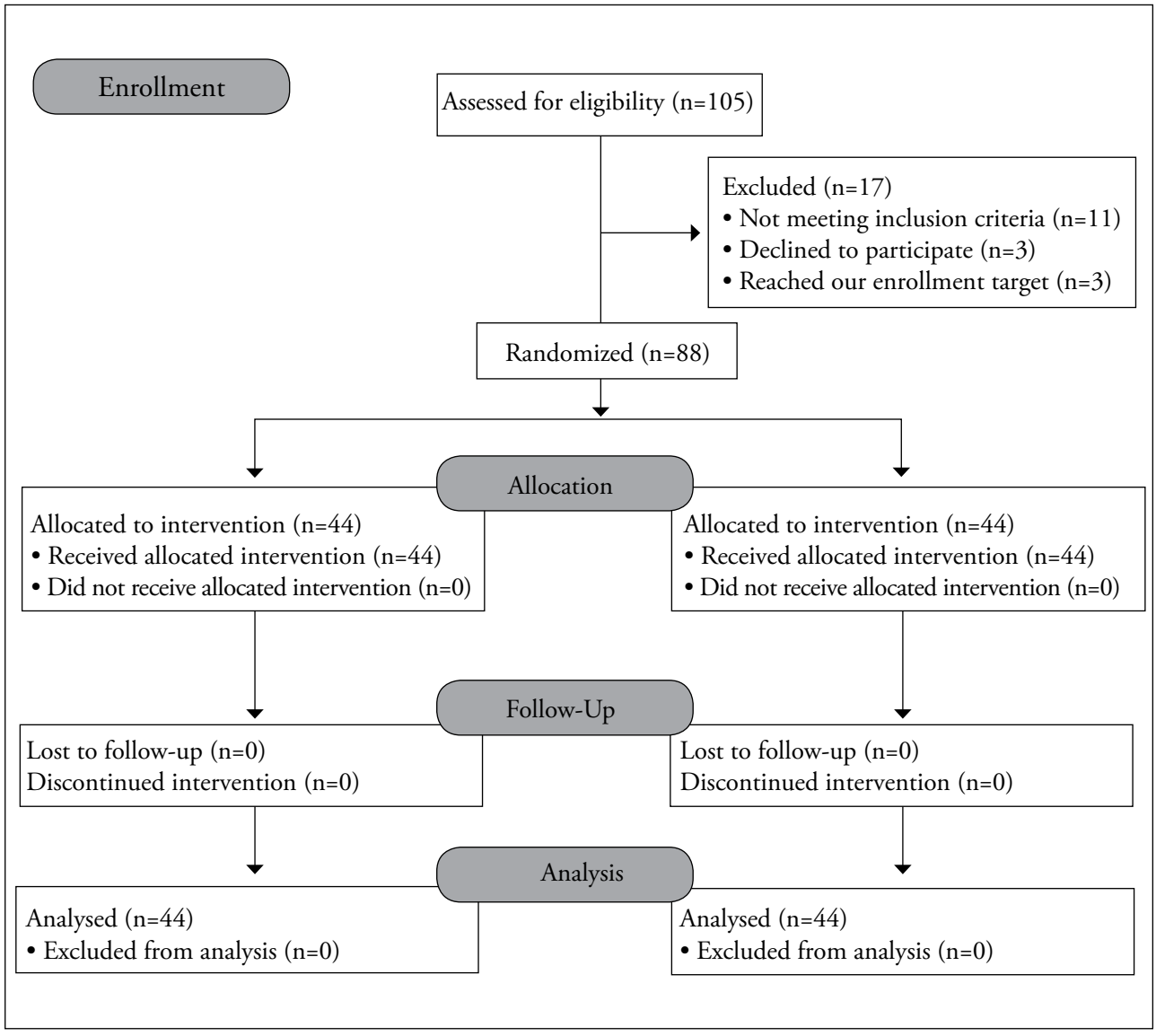

Figure 2. Consort flow diagram of the study

Table 2. Patient characteristics

Variables	MT group (n=44)	R group (n=44)	p
Age (years)	39.3±10.6	37.8±10.1	0.691
Sex (n)			
Male/Female	32/12	28/16	0.492
ASA physical state (n)			
I/II	25/19	24/20	0.999
Lund-Mackay score	10 (6-14 [3-20])	12 (8.75-15 [4-19])	0.329
Preoperative laboratory results			
Prothrombin time (s)	13.4±0.6	13.1±0.5	0.067
Partial thromboplastin time (s)	29.7±2.2	30.6±2.2	0.082
International normalised ratio	1.02±0.08	1.01±0.07	0.611
Preoperative haemoglobin (g dL^{-1})	14.2±1.3	14.1±1.3	0.659
Platelet count (10^3/mcl)	242±69	236±69	0.666

Values are expressed as numbers, median (IQR [range]) or mean±SD. There was no statistical difference between the groups. ASA: American Society of Anesthesiologists.

Table 3. Operative data and incidence of adverse haemodynamic events during surgery

Variables	MT group (n=44)	R group (n=44)	p	x^2
Duration of surgery (min)	117±25	116±30	0.839	
Duration of anaesthesia (min)	131±26	130±32	0.875	
No. of opened sinuses	5 (4-7 [1-9])	5 (3-6 [1-9])	0.352	
rSO_2 values (n)				
Baseline rSO_2 (%)	69.75±8.23	69.66±9.06	0.949	
Cerebral desaturation (n)	0	2 (5%)	0.474	0.51
Mean rSO_2 (%)	69.8±8.2	69.7±9.1	0.808	
Minimum rSO_2 (%)	53	52	0.869	
$AUCrSO_2$ <75% (%)	0±0	0.21±0.95	0.162	
Incidence of adverse haemodynamic events (n)				
Hypotension	0	3 (7%)	0.241	1.38
Bradycardia	0	18 (41%)	<0.001	20.18

Values are expressed as mean±SD, median (IQR [range]) or number. None of the patients had baseline rSO_2 values <50%. rSO_2: regional cerebral oximetry; AUC_{rSO2} <75%: area under the curve when rSO_2 values decreased <75% of the baseline

Table 4. Time spent, VAS, analgesic requests and incidence of postoperative nausea and vomiting in PACU

	MT group (n=44)	R group (n=44)	p	x^2
Mean time spent in PACU (min)	19±6	19±6	0.36	
VAS at arrival to PACU	3 (2-3 [1-6])	3 (2-6 [1-9])	0.05	15.76
VAS at discharge from PACU	4 (3-5 [1-7])	4 (3-5 [2-7])	0.55	4.92
Analgesic requests at PACU (n)	6 (14%)	14 (32%)	0.07	3.17
Incidence of nausea at PACU (n)	10 (23%)	14 (32%)	0.47	0.52

Values are expressed as mean±SD, median (IQR [range]) or number (%). VAS: visual analogue scale; PACU: post-anaesthetic care unit

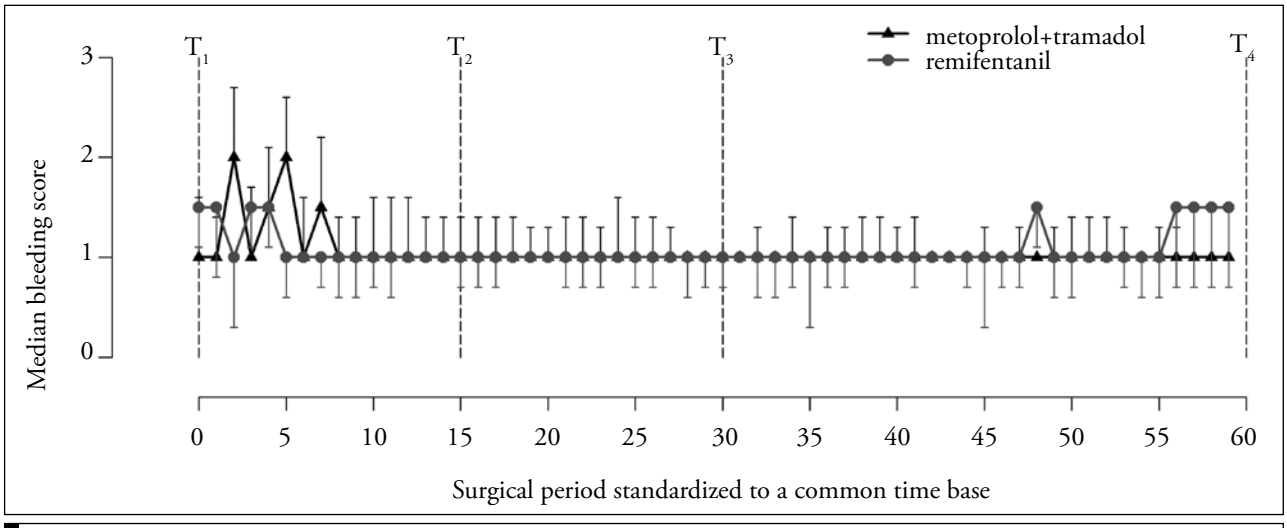

Figure 3. Graphical representation of the median intraoperative bleeding score. T1, beginning of surgery (p=0.459); T2, 15 min of surgery (p=0.242); T3, 30 min of surgery (p=0.312); T4, end of surgery (p=0.038)

These findings are consistent with Komatsu et al.'s (5) review, which reported more frequent episodes of bradycardia and hypotension with remifentanil compared to short-acting opioids in general anaesthesia. Furthermore, studies comparing remifentanil to other hypotensive agents, such as nitroprusside in FESS (14) or nitroprusside and esmolol in tympanoplasty (15), reported significantly reduced heart rates associated with the use of remifentanil for controlled hypotension.

Apart from a high incidence of bradycardia, remifentanil has additional disadvantages related to its ability to reach its peak effect rapidly following a bolus dose. Its adverse effects include hypotension, apnoea and muscle rigidity, and they have led

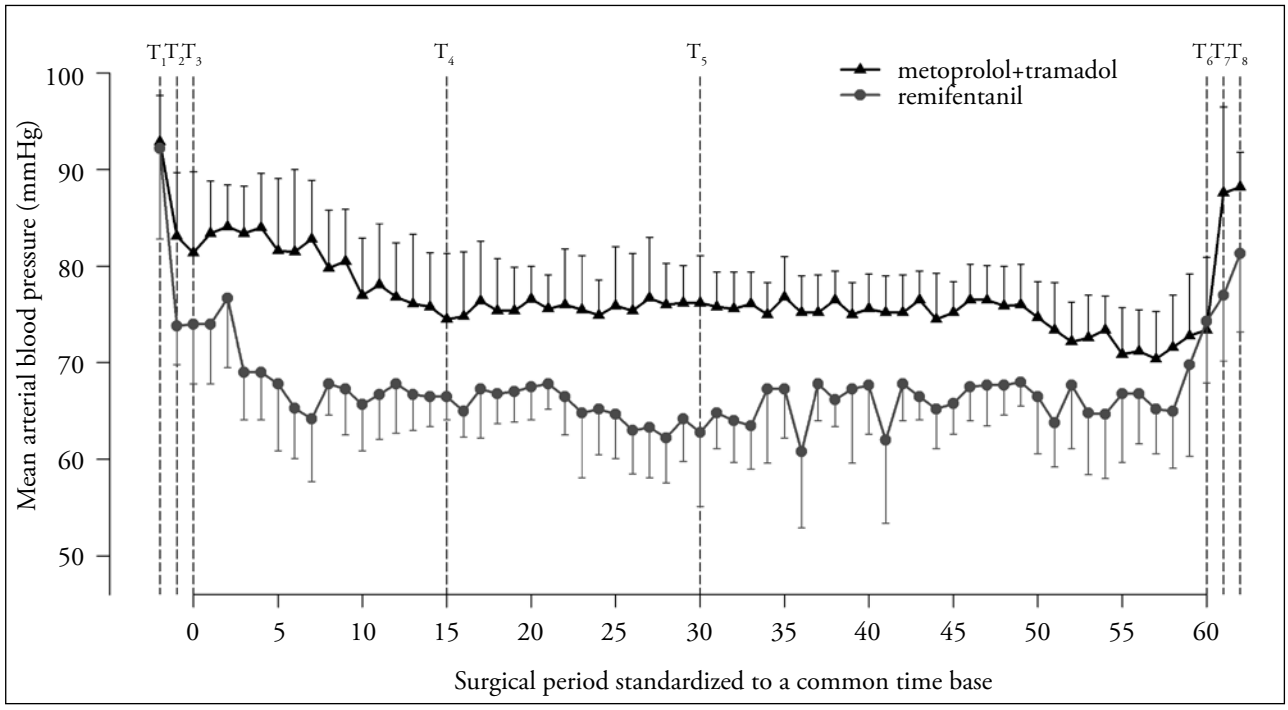

Figure 4. Graphical representation of the mean arterial blood pressure. T1, induction of anaesthesia (p=0.896); T2, intubation of the trachea (p=0.531); T3, beginning of surgery; T4, 15 min of surgery (p<0.001); T5, 30 min of surgery (p<0.001); T6, end of surgery (p<0.001); T7, after extubation of the trachea (p<0.001); T8, arrival to the post-anaesthetic care unit (p=0.985)

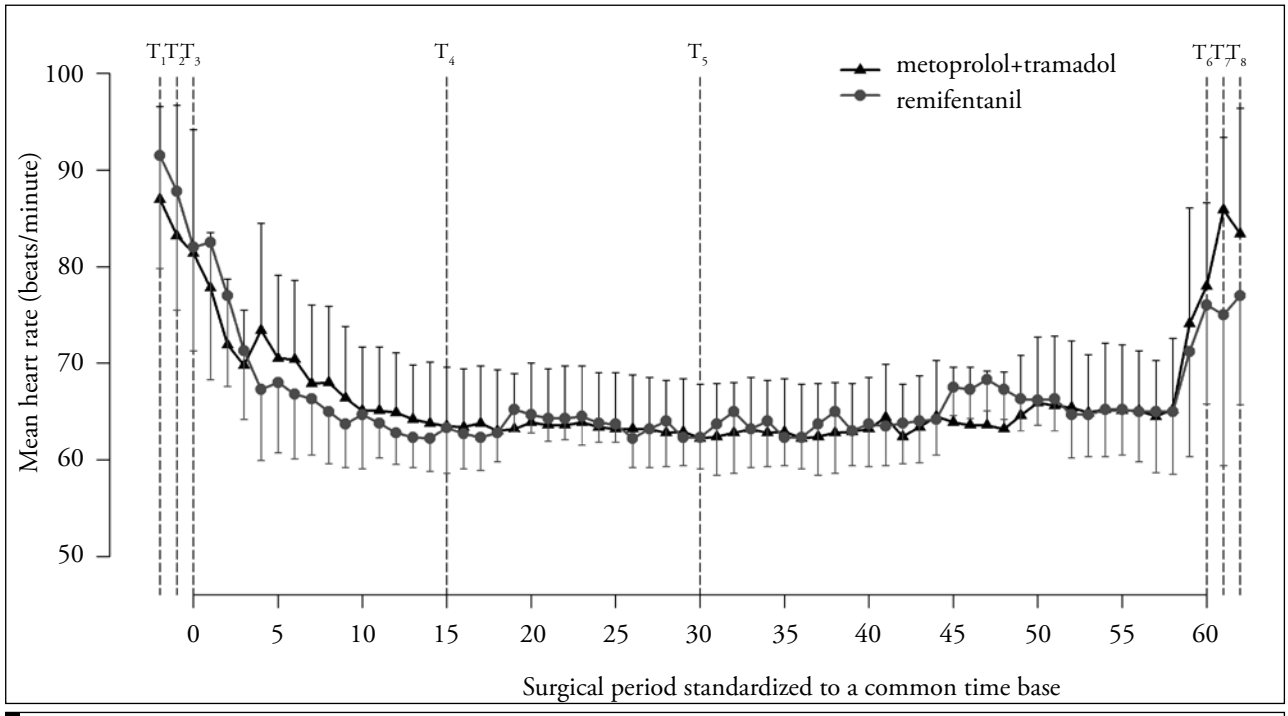

Figure 5. Graphical representation of the heart rate. T1, induction of anaesthesia (p=0.413); T2, intubation of the trachea (p=0.698); T3, beginning of surgery; T4, 15 min of surgery (p=0.697); T5, 30 min of surgery (p=0.795); T6, end of surgery (p=0.662); T7, after extubation of the trachea (p=0.228); T8, arrival to the post-anaesthetic care unit (p=0.560)

to the abandonment of bolus doses in favour of high dose rate infusions >1 min. Another subset of disadvantages is related to its second advantage, that is, its rapid, organ-independent metabolism. In case of an abrupt cessation of infusion or a pump failure, the patient may experience pain or agitation. This is not a major problem in the intraoperative period due to the co-administered anaesthetic drugs. However, there are four basic choices to maintain analgesia postoperatively: administering remifentanil in analgesic doses, administering an opioid with a longer half-life but less predisposing to apnoea,

administering a non-opioid analgesic and administering regional anaesthesia as local anaesthesia. In the institution that provided the setting for this research study, postoperative pain is usually treated with IV paracetamol, which is sufficient for pain control in most patients. Note that the present study did not try to compare the long-term postoperative analgesic effect of the two techniques, but concerned itself with the immediate postoperative period, approximately 15 min after the end of the surgical procedure.

The above-mentioned disadvantages also apply to esmolol, after which remifentanil was patterned. IV medication infusion errors are among the most common and life-threatening events (16). Unfortunately, built-in dose-checking technology and alarm limits do not protect the patient from adverse drug events when at-risk behaviours are present (17). When anaesthetists have to focus on variable rate infusions and do not have enough time for this, it is detrimental to patient safety. Since preventing adverse haemodynamic events related to variable rate continuous infusions through the use of normotensive anaesthesia was part of the present study's hypothesis, single IV doses of metoprolol were chosen over a variable rate infusion of esmolol to increase the simplicity of administration and monitoring.

There is a controversy in the literature as to whether beta blockers have any analgesic properties. When analgesia is defined in terms of reduced consumption of opioids, beta blockers appear to qualify (18, 19). However, a recent study found no analgesic effect of esmolol in the context of cold pain tolerance testing (20). In contrast with vasodilators, beta blockers, such as metoprolol and esmolol, can produce a dry surgical field without profound hypotension or bradycardia (4, 21). Whether an analgesic component exists or not, their main mechanism for decreasing surgical bleeding appears to be the inhibition of the sympathetic nervous system.

In the present study, the analgesic component was probably provided by N_2O and tramadol, which is considered a weak opioid analgesic compared to remifentanil. There is a paucity of data that compare the analgesic efficacy of tramadol alone to that of remifentanil in nasal or sinus surgery. However, Orbach-Zinger et al. (22) found that tramadol has similar or even superior patient-controlled analgesia compared to remifentanil in second trimester abortion. However, their study co-administered 10 mg IV metoprolol along with 1 mg kg^{-1} IV tramadol as a loading dose; as their first assessment of the VAS score of pain was obtained during the first 4 h post-procedure, their results may not be directly related to the present study. Tramadol was loaded >30 min in the current study, correlating with a time to peak effect of at least 20 min (23). This does not explain, however, why patients receiving metoprolol and tramadol had low heart rates and similar intraoperative bleeding scores as early as 13 min of induction, only 5 min later than patients who received remifentanil.

Although the infiltration of local anaesthesia containing 5 μg mL^{-1} epinephrine is expected to cause hypotension due to β2-adrenergic receptor activation (24), a hypertensive and bradycardic response was observed in the majority of patients in the MT group for approximately 10 min, whereas blood pressure and heart rate continued to decrease in the R group. A rapid increase in the expired desflurane concentration is known to cause tachycardia and hypertension (25), but the bradycardic response and the short duration of hypertension show no relationship with desflurane.

It is likely that the hypertensive response was related to pain caused by the infiltration of the local anaesthesia. The absence of such response in the R group might have been related to the capability of remifentanil to quickly attenuate the haemodynamic response to surgical trauma and stress or cardiovascular changes related to desflurane anaesthesia (4, 26). Orbach-Zinger et al. (22) did not discuss the possible interaction between metoprolol and tramadol; however, we believe that the analgesic efficacy of tramadol, supplemented by the indirect activation of postsynaptic α2-adrenergic receptors, may have been augmented by the metoprolol-mediated block of sympathetic outflow as suggested by Puthenveettil et al. (27).

The results of the present study suggest that the mechanism whereby intraoperative bleeding is reduced may not be induced by hypotension. The tramadol-mediated α2-adrenergic activity may explain similar degree of bleeding despite a higher mean arterial blood pressure. The nasal vasculature, including the arteriovenous anastomoses, is lined with both noradrenergic and cholinergic nerve endings. While sympathetic stimulus causes vasoconstriction in both capacitance and resistance vessels via α-adrenergic mechanism and parasympathetic stimulus causes vasodilatation via a non-cholinergic mechanism, it was shown that the result of simultaneous and balanced stimulation of the nasal vessels is vasoconstriction (28).

Cerebral desaturation was only observed in two patients for whom remifentanil infusion had to be stopped due to bradycardia and profound hypotension. Our observations are similar to those of Erdem et al. (29) who reported cerebral desaturation in 5 of the 50 patients in their study. They used propofol, remifentanil and nitroglycerin to induce hypotensive anaesthesia in patients with an ASA physical status of 1 and observed cerebral desaturation when the mean blood pressure dropped <60 mmHg. These findings demonstrate that controlled hypotensive anaesthesia with vasodilator drugs may be deleterious for cerebral oxygenation.

Since hypotension decreases tissue perfusion, the best candidates for controlled hypotension are normotensive patients with no comorbidities. Owing to the possible deleterious effects of hypoperfusion, it is important to protect the haemodynamic parameters within each patient's physiological limits. For patients with stenotic arteries or chronic hypertension, the general recommendation is to maintain the mean blood pressure as close as possible to the baseline values (30,

31). Sieskiewicz et al. (32) studied operative field conditions in patients with a heart rate of approximately 60 beats min^{-1}. They reported that in approximately 40% of these patients, good operative field conditions exist at a mean arterial pressure >65 mmHg. Their study hints at the possibility that among the haemodynamic parameters, bradycardia is more significant in an intraoperative context; aiming for hypotension is not feasible for patients with comorbidities.

Study limitations

Since there are insufficient studies comparing the intraoperative use of metoprolol and remifentanil in the literature, the discussion about metoprolol's potential contribution to the outcome made heavy use of studies on esmolol.

Another limitation of the present study is the small sample size, with only 44 participants enrolled in each study group. However, this number was calculated prior to recruitment. As this is a pilot study, these values are more than enough to achieve the research goals and prove that normotensive analgesia using single doses of intravenous beta blockers and opioids is an area worth investigating.

Conclusion

The present study indicates that providing sufficient analgesia with tramadol and eliminating the stress response with metoprolol can provide a stable heart rate and a good surgical field with no need for additional hypotension. Considering the significant predictors of bleeding (duration of surgery and severity of sinonasal disease), normocapnia and the efficacy of the surgical technique and the local decongestants (33), preventing haemodynamic adverse effects may be preferable to maintaining meticulous control of the haemodynamic parameters.

Future studies investigating the advantages of this technique for patients with stenotic arteries or ischaemic organ diseases are needed.

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