European Archives of Oto-Rhino-Laryngology (2019) 276:3095–3104
https://doi.org/10.1007/s00405-019-05575-6

RHINOLOGY

Randomized clinical trial to compare the efficacy to improve the quality of surgical field of hypotensive anesthesia with clonidine or dexmedetomidine during functional endoscopic sinus surgery

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Received: 14 April 2019 / Accepted: 16 July 2019 / Published online: 30 July 2019

Abstract

Purpose Intense bleeding of the surgical field is a potential factor influencing success of functional endoscopic sinus surgery (FESS). Hypotensive anesthesia with α2 intravenous agonists reduces intraoperative bleeding, but which is the best agent is unknown. The main objective of this trial was to compare the current standard adjuvant drug for hypotensive anesthesia, clonidine, with the recently available alternative dexmedetomidine.

Methods A randomized clinical trial compared the efficacy of clonidine and dexmedetomidine during FESS. Treatment was open label for the anesthesiologist and operating surgeon, but blind for an external evaluator who evaluated video-recorded surgeries. A Boezaart scale was assessed every 30 min during FESS until surgery completion. Main end-point was the proportion of patients with mean Boezaart scores > 2 (heavy bleeding) by external blinded evaluator. Secondary end-points included other bleeding parameters, surgery duration, hemodynamic measures and surgical complications.

Results 94 patients were randomized. There were no significant differences in the proportion of patients with mean Boezaart scores > 2 in clonidine (42.6%) and dexmedetomidine (42.6%). Consistently, no differences were observed in secondary variables of bleeding, duration or complications. Small differences in mean heart rate were observed that might reflect different pharmacological profiles of the products, but are of uncertain clinical relevance.

Conclusions No significant differences were observed between clonidine and dexmedetomidine when used as anesthetic adjuvants in the reduction of surgical bleeding in FESS. A longer experience with clonidine and its lower costs suggest it may be a preferable option as an adjuvant for hypotensive anesthesia.

Keywords Functional endoscopic sinus surgery · Adrenergic α2-receptor agonists · Clonidine · Dexmedetomidine · Surgical blood loss

Introduction

Endoscopic sinus surgery is minimally invasive, fast and safe, but the outcome may be strongly dependent on the surgical field conditions [1, 2]. Excessive bleeding compromises surgical field visibility, makes more difficult the identification of anatomical landmarks and increases the risk of harming the surrounding structures. Uncontrolled bleeding also significantly increases surgical time [3, 4]. Therefore, it is of utmost importance to minimize bleeding.

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Several approaches have been tested to reduce intraoperative bleeding, including non-pharmacological measures, such as the reverse Trendelenburg position of the patient, or the use of pharmacological adjuvants, such as preoperative corticosteroids to reduce inflammation, injection of adrenaline in the diseased mucosa prior to surgery, administration of intravenous or topical tranexamic acid, or repeated packing with cottonoids soaked in adrenaline during surgery [5–9]. Also, controlled hypotension during surgery can be induced using an anesthetic regimen including hypotensive agents, such as α2 adrenergic agonists (A2AA) (dexmedetomidine or clonidine). A2AA act mainly in the central nervous system, where the stimulation of α2 receptors induces hypotension, analgesia and sedation [10, 11]. Clonidine is a well-known and cheap drug that has been used for decades in hypertension in different clinical circumstances [12]. Dexmedetomidine, a highly selective A2AA compound, has been available in the United States since 1999, but only recently introduced in the European market: first in 2011 for sedation in non-intubated patients prior to and/or during surgery, and 7 years later as an anesthetic adjuvant [13].

The interest for using A2AA as adjuvant anesthetics for the reduction of surgical field bleeding in endoscopic sinus surgery has been renewed paralleling the conduction of a number of clinical studies. Besides, there are relevant cost differences between A2AA drugs. A systematic review carried out by our research group [14] concluded that A2AA consistently reduced intraoperative bleeding and improved the surgical field quality during endoscopic surgery, although their use did not decrease the average length of surgery, and there was not enough data to conclude on whether this may reduce surgical complications. The comparative information was scarce and heterogeneous, so that it was insufficient to conclude on potential differences in efficacy or adverse events amongst treatments.

Pharmacological differences in selectivity in front of alpha-adrenergic receptor subtypes between clonidine and dexmedetomidine suggest that they might perform clinically differently; while dexmedetomidine is highly selective for α2 receptors, a partial agonist effect on α1 receptors of clonidine could determine better control of bleeding in peripheral vessels [10–12]. There were no published trials comparing both drugs since the only available randomized comparison of intravenous dexmedetomidine and clonidine [15].was published only once our trial was ongoing. Because of that, we designed a prospective randomized, double-blind clinical trial with the aim of obtaining clinical evidence on a potentially different effect of clonidine versus dexmedetomidine on surgical field bleeding during FESS.

Materials and methods

A randomized, double-blind trial was designed to compare intraoperative surgical field bleeding of two A2AA drugs, clonidine and dexmedetomidine, as anesthetic hypotensive adjuvants in FESS. Our working hypothesis was that clonidine would be associated with less intraoperative bleeding than dexmedetomidine. The study was authorized by the Ethic's Committee of Corporació Sanitària Parc Taulí and by the Spanish Agency of Medicines and Medical Devices, and registered in EudraCT with number 2015-002102-37 before first patient inclusion. Informed consent was obtained from all individual participants included in the study before any study-related procedure.

Patients

Patients were eligible if they were aged 18 years or older, were programmed for FESS due to chronic rhinosinusitis (CRS) with or without nasal polyposis, had an ASA score (American Society of Anesthesiologists Physical Status Scale Ratings) I–III, and provided signed informed consent before surgery. Patients were excluded if they had contraindications for either FESS or any of the studied anesthetic regimens or drugs, presented coagulation disorders, previous history of coronary arteriopathy, stroke or arrhythmia, or had recently received or currently on adrenergic or calcium channel blockers, anticoagulants or NSAIDs ("recently" being considered as a period of less than seven half-lives of the drug). Randomization to each of the arms was done in blocks and stratified by the center where surgery was performed and by surgery indication (either chronic rhinosinusitis, or chronic rhinosinusitis with nasal polyposis). Individual sealed codes were prepared at the Clinical Pharmacology Department according to a randomization list, using the Winpepi version 2.67: Balanced stratified (module A4) [16]. The list and a copy of the codes were kept safely and separately in a file that was not accessible either to surgeons or to anesthetists. Patients were randomly allocated on arriving to the operating room by the anesthesiologist, who opened the first available sequentially numbered sealed code within the patient stratum. Treatment allocation was deemed open-label for the anesthesiologist and operating surgeon since dexmedetomidine administration required an infusion pump difficult to mask, but treatment identity was kept blind for an external evaluator who assessed bleeding in the surgical field through video recordings.

Treatments

Treatment consisted of either a single intravenous dose of 1–1.5 micrograms (μg) per kilogram (kg) of clonidine in saline infusion (100 ml) 20 min before the initiation of the surgery, or a bolus of dexmedetomidine of 1 μg/kg followed by a maintenance dose of 0.2–1 μg/kg/h, titrated according to sedation, during the procedure (1 ampule of dexmedetomidine 2 ml diluted in 48 cc of saline infusion). In addition to the treatments studied, patients received anesthesia according to the center's standardized local protocols, consisting of a balanced anesthetic induction with 4 milligrams (mg) per kg of propofol and 2–3 μg per kg of fentanyl, a non-depolarizing neuromuscular blocking drug, and anesthetic maintenance with sevoflurane. Premedication included 4 mg of dexamethasone and ondansetron as prophylaxis of nausea and vomiting, and midazolam could be used if required at the discretion of the anesthesiologist. All patients received intraoperative prophylaxis with a single dose of 1 g co-amoxiclav (or 300–600 mg of clindamycin in case of allergy to betalactams). Our standard routine protocols do not include any preoperative anti-inflammatory medication. Three ENT and four anesthesiologists performed the surgical and anesthetic procedures of the study patients in two different centers (Hospital de Sabadell-Sabadell, Barcelona and Clínica del Vallés-Sabadell, Barcelona).

Assessments

Surgical field bleeding was evaluated by both the operating surgeon and an external rhinologist (blinded) who reviewed the complete records of the surgical intervention. Every 60 min, the surgical field was assessed by two subjective methods: the Boezaart surgical field bleeding score [17] and a visual analogue scale (VAS). Interventions were videotaped with a camera coupled to the endoscope, and sent in batches of ten recordings to an external investigator who was blinded to patient and treatment identity for evaluation of bleeding using the same Boezaart score and the VAS at the predefined time points. Video recordings were assessed by three surgeons, who assessed surgeries in which they had not been present.

The main variable was the proportion of patients with intense bleeding, defined as a mean Boezaart score above two during surgery as assessed by the external investigator. Other objective outcome measures included the estimated amount of blood loss, derived from the volume and hemoglobin of the fluid aspirated during surgery. This value was corrected by the patient's mean hemoglobin, according to the formula Hba (g/dl) × *V* (ml)/Hbm (g/dl), where Hba represents the hemoglobin of the fluid aspirated from the surgical field, *V* the total volume of the aspirated fluid and Hbm the patient's mean hemoglobin considering pre- and postoperative values [18]. Other secondary outcomes included the duration of surgery and anesthesia, and safety assessments including hemodynamic parameters [systolic and diastolic blood pressure (SBP and DBP)], mean blood pressure (MBP) and heart rate (HR) as measured every 15 min, and ventilation (CO_2 at the end of procedure). Adverse events (complications) were also registered. Potentially relevant baseline characteristics for prognosis were collected, including sinus occupancy based on the Lund–Mackay scale (0–24 points) [19], extent of disease (polyposis grading I–IV), presence or absence of Widal's triad, previous history of asthma, concurrent pharmacological treatment and other medical diseases. Patients were followed until hospital discharge and 1 week later. Postoperative clinical outcomes included time to patient discharge, need to return to hospital for surgery-related complications, need for re-operation, and any late adverse events.

Statistical analysis

A sample size of 47 patients per group was calculated to ensure a protection against type 1 error of 5% and an 80% power to detect differences in the main outcome [dichotomized mean Boezaart value (2 or lower vs higher than 2) as assessed by the external surgeon] of 25% or bigger, and assuming a proportion of heavy bleeding of 15% in clonidine, based on a previous study [20]. The main outcome was compared using a Fisher's exact test for differences between groups and considering the randomization strata. Qualitative variables were described by the number of valid values and the frequency and percentage of each category, and compared between groups using Fisher's exact tests. Quantitative variables were described by measures of central tendency and dispersion, and compared between groups using analysis of variance (ANOVA). Variables measured at different time points (Boezaart scale each 60 min and SBP, DBP, MBP and HR every 15 min during the intervention) were analyzed using a stratum- and baseline-adjusted repeated measurement analysis. The main analysis was done by intention to treat (ITT) on all dosed patients, using the full analysis set.

Results

All patients undergoing elective FESS due to chronic rhinosinusitis with or without polyps in our service between November 2015 and June 2017 were considered for eligibility, and 96 potentially eligible were informed for consent; all but one accepted to participate so that 95 patients were randomized. For one patient, an exclusion criterion was detected after randomization, and was not dosed. There were no losses to follow-up (Fig. 1).

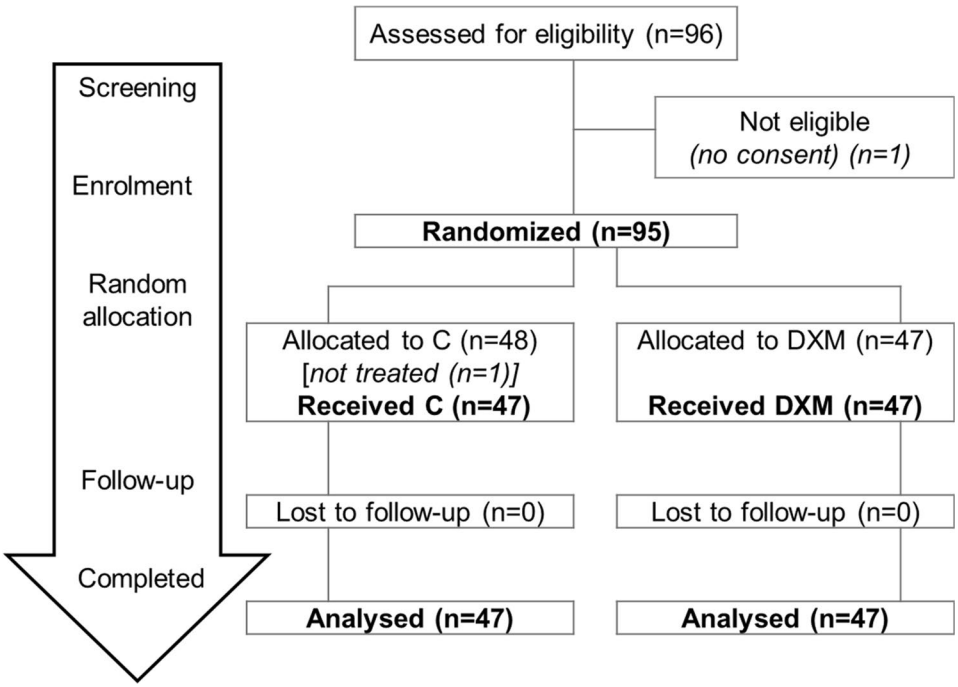

Fig. 1 Study flowchart

Baseline characteristics were well balanced between the groups; the degree of radiological severity of the CRS, based on the Lund–Mackay scale [19], showed average [standard deviation (SD)] scores of 13. 0 (7.8) and 13.5 (6.8) for clonidine and dexmedetomidine, respectively. The most frequent indication for performing endoscopic surgery was chronic rhinosinusitis with nasal polyposis (70% in both groups), of which roughly half corresponded to grade IV polyposis (19 in clonidine and 16 in the dexmedetomidine), indicating high surgical complexity [21–23]. Consistently, most surgeries were bilateral, and 31 cases (66%) in clonidine group and 37 (78.7%) in dexmedetomidine group required posterior ethmoidectomy and sphenoidotomy in addition to the previous ethmoidectomy. Septoplasties were done in addition to FESS in 43 cases. Six cases in the clonidine group and seven in the dexmedetomidine group were re-interventions (Table 1).

No significant differences were observed in the proportion of patients that had an average value of the Boezaart scale > 2 (heavy bleeding) as assessed by the external evaluator (20 cases (42.6%) in clonidine and 20 cases (42.6%) of dexmedetomidine group). No differences were observed either in any of the secondary outcome measures. (Table 2). No differences were observed in the mean (SD) volumes of aspirated fluid [clonidine 468 (416.6) ml and dexmedetomidine 363.4 (312.4) ml] nor in the mean (SD) calculated blood volume loss according to the Hb correction formula [136.0 (138.7) ml in dexmedetomidine and 216.7 (266.) ml in clonidine].

Regarding safety, hemodynamic parameters confirmed hypotension and reduced heart rate without reaching bradycardia, suggesting lower heart rate values in patients treated with dexmedetomidine, with differences at 30′, 45′, 60′ and 75′ after the start of surgery [mean (SD) values of 68.5 (10, 46), 70.3 (12, 15), 71.5 (11, 44) and 70.5 (11, 23) bpm in clonidine group compared to 61.3 (9, 98), 61.7 (9, 03), 62.4 (8, 18) and 63.7 (9, 56) bpm in dexmedetomidine group] that were statistically significant at 30′ ($p < 0.01$), 45′ ($p < 0.00$), 60′ ($p < 0.00$) and 75′ ($p < 0.04$). Systolic, diastolic and mean blood pressure remained low throughout surgery and with no substantial nor significant differences between both drugs (Fig. 2). End-of-surgery mean (SD) CO_2 was 34.6 (4, 13) and 33.9 (3, 89) mmHg in clonidine and dexmedetomidine groups, respectively, with no significant differences. No adverse reactions attributable to study medications were observed.

The mean (SD) duration of surgery was 110.7 (40, 94) and 103.8 (37, 19) minutes in clonidine and dexmedetomidine, respectively, and the mean (SD) duration of anesthesia was 148.6 (45, 03) in clonidine and 145.6 (42, 2) in dexmedetomidine group. There were no significant differences in either variable. In each group, there was a patient with bleeding, who required medical attention. No patient required surgical re-intervention.

Discussion

The presence of significant bleeding in the surgical field is a critical factor in the success or failure potential in FESS. When copious bleeding occurs, the recognition of surgical

Table 1 Baseline characteristics of patients

Analyzed variable	Clonidine $N=47$	Dexmedetomidine $N=47$	Total $N=94$
Sex: male (%)	31 (66.0%)	36 (76.6%)	67 (71.3%)
Age mean (± SD)	47.60 (11.0)	48.02 (10.51)	47.81 (10.70)
BMI mean (± SD)	26.86 (6.2)	27.30 (6.3)	27.08 (6.2)
Asthma (%)	9 (19.1%)	8 (17.0%)	17 (18.1%)
Widal's triad (%)	1 (2.1%)	2 (4.3%)	3 (3.2%)
ASA class (%)			
1	15 (31.9%)	11 (23.4%)	26 (27.7%)
2	30 (63.8%)	35 (74.5%)	65 (69.1%)
3	2 (4.3%)	1 (2.1%)	3 (3.2%)
Surgical indication			
CRSsNP	14 (29.8%)	14 (29.8%)	28 (29.8%)
CRSwNP	33 (70.2%)	33 (70.02%)	66 (70.2%)
Grade I	1 (2.1%)	1 (2.1%)	2 (2.1%)
Grade II	6 (12.8%)	8 (17%)	14 (14.9%)
Grade III	7 (14.9%)	8 (17%)	15 (16.0%)
Grade IV	19 (40.4%)	16 (34%)	35 (37.2%)
Lund–Mackay score mean (± SD)	13.00 (7.80)	13.47 (6.82)	13.21 (7.29)
Type of FESS			
Anterior ethmoidectomy with medial meatotomy	42 (89.4%)	45 (95.7)	87 (92.6%)
Posterior ethmoidectomy ± sphenoidotomy	31(66%)	37 (78.7%)	68 (72.3%)
Septoplasty	23 (48.9%)	20 (42.6%)	43 (45.7%)
Unilateral surgery	12 (25.5%)	8 (17.0%)	20 (21.3%)
Bilateral surgery	35 (74.5%)	39 (83.0%)	74 (78.7%)
Primary surgery	41 (87.2%)	40 (85.1%)	81 (86.2%)
Reoperation surgery	6 (12.8%)	7 (14.9%)	13 (13.8%)
Center			
Clínica del Valles	12 (25.5%)	11 (23.4%)	23 (24.5%)
Parc Taulí	35 (74.5%)	36 (76.6%)	71 (75.5%)

ASA American Society of Anaesthesia, *BMI* body mass index, *CRSsNP* chronic rhinosinusitis without nasal polyposis, *CRSwNP* chronic rhinosinusitis with nasal polyposis

anatomical references becomes more difficult, increasing the risk of complications.

For proper control of intraoperative bleeding, various strategies have been adopted, both prior to and during surgery. A preoperative antibiotic treatment and the use of steroids have been suggested and studied as measures to reduce the inflammatory and infectious component and with it the bleeding. During surgery, the elevation of the patient's head, the injection of adrenaline into the nasal mucosa, the use of topical vasoconstrictors, antifibrinolytic agents and the use of hemostatic materials are all used as intraoperative maneuvers to reduce surgical bleeding in FESS [24–29].

Among the various strategies, it has been described that anesthetic agents can also influence the volume of blood loss and the condition of the surgical field through its hypotensive or vasodilator action [30–32].

In endoscopic surgical procedures, opioid-derived anesthetics such as fentanyl, remifentanil and alfentanil, sedatives such as propofol, non-depolarizing muscle relaxant agents such as rocuronium, in a balanced anesthesia, and dexamethasone as a prophylactic of nausea and vomiting are used in routine clinical practice. Anti-hypertensive agents, such as angiotensin-converting enzyme inhibitors, nitroprusside, nitroglycerin, β-adrenergic blockers or A2AA, can be added to anesthesia to avoid copious intraoperative bleeding, maintaining a sustained and stable situation of controlled hypotension [33, 34].

There is controversy between which are the most suitable anesthetic adjuvant drugs for use during FESS. In general, those that reduce sympathetic tone at the central level and achieve relative bradycardia, improving the surgical field, would be desirable, unlike peripheral vasodilators that produce reflex tachycardia. The evaluation of the different drugs suggests that A2AA are especially interesting as anesthetic adjuvants due to their regulatory effect at the central, analgesic and sedative levels [34–38].

Table 2 Study outcomes

Analyzed variable	Clonidine $n=47$	Dexmedetomidine $n=47$	Total $n=94$
% of patients with average value of Boezaart scale > 2 (heavy bleeding) (number of observations available) (p value for main outcome)			
External evaluator (main variable)	20 (42.6%) ($n=47$)	20 (42.6%) ($n=47$)	40 (42.6%) ($n=94$) $p=0.58$
Operating surgeon	23 (48.9%) ($n=47$)	22 (46.8%) ($n=47$)	45 (47.9%) ($n=94$) $p=0.50$
Average (SD) value of Boezaart score (number of observations available)			
External evaluator (1 min)	2.21 (0.59) ($n=47$)	2.19 (0.65) ($n=47$)	2.20 (0.62) ($n=94$)
Operating surgeon (1 min)	2.19 (0.61) ($n=47$)	2.23 (0.63) ($n=47$)	2.21 (0.62) ($n=94$)
External evaluator (60 min)	2.21 (0.71) ($n=43$)	2.25 (0.54) ($n=40$)	2.23 (0.63) ($n=83$)
Operating surgeon (60 min)	2.33 (0.81) ($n=43$)	2.29 (0.51) ($n=41$)	2.31 (0.68) ($n=84$)
External evaluator (120 min)	2.24 (0.44) ($n=20$)	2.20 (0.52) ($n=21$)	2.22 (0.48) ($n=41$)
Operating surgeon (120 min)	2.35 (0.59) ($n=20$)	2.29 (0.46) ($n=21$)	2.32 (0.52) ($n=41$)
External evaluator (180 min)	2.00 (0.00) ($n=2$)	2.00 (–) ($n=1$)	2.00 (0.00) ($n=3$)
Operating surgeon (180 min)	2.00 (0.00) ($n=2$)	2.00 (–) ($n=1$)	2.00 (0.00) ($n=3$)
Average (SD) value for visual analogue scale of bleeding (number of observations available)			
External evaluator (1 min)	2.69 (1.42) ($n=47$)	2.43 (1.19) ($n=47$)	2.56 (1.31) ($n=94$)
Operating surgeon (1 min)	2.68 (1.29) ($n=47$)	2.62 (1.24) ($n=47$)	2.65 (1.26) ($n=94$)
External evaluator (60 min)	2.80 (1.57) ($n=43$)	2.67 (1.31) ($n=40$)	2.74 (1.45) ($n=83$)
Operating surgeon (60 min)	3.14 (1.84) ($n=43$)	2.77 (1.57) ($n=41$)	2.96 (1.71) ($n=84$)
External evaluator (120 min)	2.89 (1.23) ($n=21$)	2.58 (1.40) ($n=20$)	2.74 (1.31) ($n=41$)
Operating surgeon (120 min)	3.28 (1.32) ($n=20$)	2.53 (1.45) ($n=21$)	2.9.0 (1.46) ($n=41$)
External evaluator (180 min)	2.30 (0.56) ($n=2$)	1.5.0 (–) ($n=1$)	2.03 (6.11) ($n=3$)
Operating surgeon (180 min)	2.30 (0.14) ($n=2$)	2.0 (–) ($n=1$)	2.20 (2.00) ($n=3$)

SD standard deviation, *pp* value, *n* number of observations

Clonidine has been used in our center for 9 years, with good results [39] that prompted us to confirm its efficacy through a randomized clinical trial comparing clonidine with our previous standard (remifentanil), concluding substantially less surgical bleeding during FESS with clonidine [20].

Dexmedetomidine is distinguished from clonidine in a higher selectivity by α2 receptors and had been evaluated as an anesthetic adjuvant in FESS in other countries where it was authorized in this indication [40–43]. In Europe, dexmedetomidine was introduced as a sedative agent, and has been recently authorized as adjunctive anesthetic. The more selective pharmacological profile of α2 receptors theoretically could lead to better sedation and greater hypotension of dexmedetomidine compared to clonidine, but, on the other hand, we believed that it could be associated with a worse result in terms of intraoperative mucosal

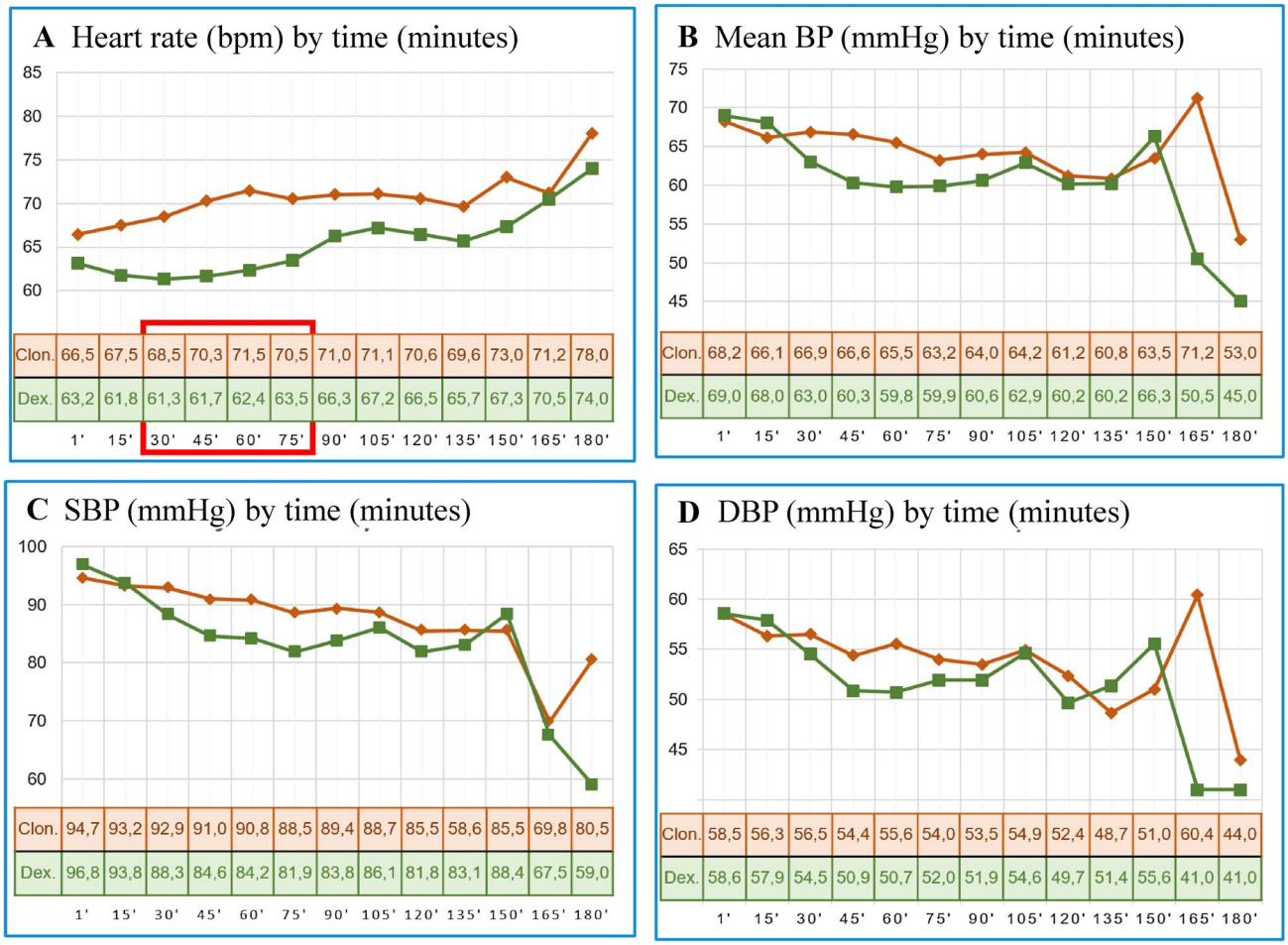

Fig. 2 Hemodynamic parameters. *bpm* beats per minute, *BP* blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure. Red line: clonidine; green line: dexmedetomidine

bleeding, associated with a nonspecific α-agonist effect of clonidine, and is an expensive drug.

The availability of a new therapeutic alternative prompted us in 2016 to design a trial to test both drugs to know which of the two A2AA could provide better results. The study by Das et al. [15] was published while our study was already ongoing.

We did not observe any differences between treatments in the main outcome, nor in any of the secondary efficacy outcomes of the study, including objective assessment of bleeding through surgical aspirate. The study was powered to detect differences of 25% or higher between treatments, and used a design similar to the previous trial of our group, which was able to detect differences between clonidine and remifentanil. The open-label design with blinded evaluator has proven previously to be reasonably robust. We met the intended sample size, and randomized 94 patients undergoing elective FESS. It is possible that we would have found significant differences between treatments if the sample size had been larger, but the design of the study was based on the detection of a difference whose magnitude was defined as relevant a priori. Considering that a suitably sized sample size calculation was performed to guarantee a power of 80%, it is possible that the absence of differences is due to chance, although the protection of the study against the risk of this occurring is usually considered acceptable in clinical trials.

We observed higher than expected bleeding scores with clonidine. This may be due to the fact that the included patients had chronic rhinosinusitis, with or without sinonasal polyposis, with overall scores suggesting high severity and risk of intense bleeding during the FESS [21–23], as compared to other studies. A high-risk population was appropriate, since a low severity and intensity of bleeding would prevent distinguishing relevant differences between drugs. The doses used of both drugs were selected based on the literature review of the published articles [15, 40, 41, 43–45], and the product information.

Safety was also similar, except for some statistically significant differences in heart rate at 30, 45, 60 and 75 min. These differences, according to the participating

anesthesiologists, may be due to the fact that dexmedetomidine was administered in an open-label way during surgery, with titration according to patient's response. In their criteria, such differences do not have any clinical relevance from the hemodynamic or safety point of view, have not been related to better efficacy results, and are, therefore, irrelevant to the selection of one or the other drugs.

We have not seen any differential effects on complications either. This is consistent with the absence of intraoperative differences, although the complications are not exclusively a consequence of greater bleeding or having a better surgical field, and no previous studies have been able to show differences on postoperative complications.

The trial of Das et al. compared clonidine versus dexmedetomidine intravenously in FESS, and showed significant differences between both drugs in favor of dexmedetomidine, which provided greater hypotension and analgesia, and a lower surgical bleeding and greater satisfaction of the surgeon,, although no differences were observed in duration of surgery or anesthesia [15]. However, the main objective of the trial was to compare the efficacy of individual preoperative boluses of both drugs to achieve hypotensive anesthesia, and only secondarily tested its effects on surgical bleeding or visibility in the surgical field, amongst other secondary variables. No hierarchical approach to the analysis or multiplicity adjustment was reported that allowed considering surgical field variables as key secondary assessments, and thus from a statistical point of view, these results should be regarded as exploratory only. Clinical parameters relevant to interpret bleeding results, such as the degree of polyposis, or whether the surgery was unilateral or bilateral, were not reported, and the dexmedetomidine dosing schedule is very different from the one used in other trials, without continued intraoperative perfusion [15]. Only one surgeon did the assessments, as compared to our trial, where ratings were done both by the operating surgeons and an external surgeon blind to the study treatment. Because of that, the present trial may be considered as more adequate to answer our hypothesis.

More recently, another randomized study compared both drugs in CENS including 40 patients [46]. Ray et al. concluded that clonidine achieves less surgical bleeding and a greater reduction in blood pressure than dexmedetomidine. However, the study compared an oral dose of 2 µg/kg of clonidine as compared to 1 µg intravenous dexmedetomidine bolus followed by 0.5 µg/kg/h maintenance dose, which are quite different from our single intravenous dose of 1–1.5 µg kg of clonidine, and to the 1 µg/kg bolus of dexmedetomidine followed by a maintenance dose of 0.2–1 µg/kg/h, titrated according to sedation. The trial does not include details on randomization nor blinding, and does not report on sample size calculations or other relevant methodology aspects.

Our starting hypothesis was the superiority of clonidine to dexmedetomidine in the control of surgical bleeding, but we were not able to reject the null hypothesis of lack of differences. An important limitation of our study is that we could have designed a no inferiority study, so that we could have formally ruled out clinically important differences. Yet, based on our results, it seems that both A2AAs drugs, used as hypotensive, seem to allow a low surgical bleeding during FESS in a population with baseline characteristics associated with high risk of bleeding. Considering the same efficacy for the studied A2AA, we cannot recommend any above the other. Therefore, more practical reasons led us to suggest clonidine: its low cost and a long-lasting clinical experience, as well as the ease of use with a single dose that avoids a medical drug pump.

In conclusion, no significant differences have been observed between clonidine and dexmedetomidine when used as anesthetic adjuvants in the reduction of surgical bleeding in FESS. A longer experience with clonidine and its lower costs suggest it may be a preferable option as an adjuvant for hypotensive anesthesia.

Acknowledgements Surgery and data collection: A. Martínez, A. Aguilà, J.J. Díaz, A, M. Campos, E. Bargués, R.Rosell (Dept. of Otorhinolaryngology, Hospital de Sabadell, Institut Universitari Parc Taulí, Universitat Autònoma de Barcelona, Sabadell (Barcelona), Spain; anesthesia and data collection: J. Marco, J. Zancajo, C. Hernández, G. Marrero (Dept. of Anaesthesia, Hospital de Sabadell, Institut Universitari Parc Taulí, Universitat Autònoma de Barcelona, Sabadell (Barcelona), Spain; C.Libertad (Dept. of Anaesthesia, Clinica del Vallés)

Author contributions YE: principal investigator, study design, data collection, and manuscript writing; AC: study design and analysis, and manuscript writing; LS, SL, and AI: collaborating investigators and manuscript review; RV and MF: study monitoring and statistical analysis, and manuscript review; CP and MB: study design and analysis, project direction and manuscript writing, and both contributed equally as senior authors.

Funding The authors declare that public grants were received to conduct the present research [Fundació Parc Taulí, Sabadell (Barcelona), Spain: Beques Taulí de Recerca i d'Innovació 2014 i 2017 (CIR 2014/055, CIR2017/030)].

Compliance with ethical standards

Conflict of interest They have no other conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee (Ethics Committee of Corporació Sanitària Parc Taulí and Spanish Agency of Medicines and Medical Devices, with reference EudraCT 2015-002102-37) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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