J Anesth (2014) 28:70–75
DOI 10.1007/s00540-013-1660-2

ORIGINAL ARTICLE

Effect of clonidine added to lidocaine for sub-Tenon's (episcleral) anesthesia in cataract surgery

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Received: 26 June 2012 / Accepted: 12 June 2013 / Published online: 25 June 2013

Abstract
Purpose We aimed to evaluate the duration of anesthesia, analgesia and ocular akinesia of clonidine added to lidocaine in sub-Tenon's anesthesia in patients undergoing cataract surgery.
Methods Forty patients were prospectively enrolled. They were randomized to two sub-Tenon's anesthesia groups: group L (6 ml of lidocaine 2 %, 1 ml of 0.9 % saline and 25 UI/ml of hyaluronidase), and group C (6 ml lidocaine 2 %, clonidine 1 μg/kg, 1 ml of 0.9 % saline and 25 UI/ml of hyaluronidase). Duration of sensory anesthesia, ocular akinesia in all directions, akinesia of the levator palpebrae superioris and orbicularis oculi muscles, the duration of analgesia (time to the first postoperative use of analgesics), the overall use of analgesics and the presence of adverse effects were recorded.
Results The duration of sensory anesthesia and akinesia of the four rectus, levator palpebrae superioris, and orbicularis oculi muscles was significantly longer in group C ($p < 0.05$). The number of patients who required analgesics was similar between the groups but the duration of analgesia was longer in group C ($p < 0.05$). No significant adverse effects were observed.
Conclusion The addition of clonidine 1 μg/kg to 2 % lidocaine in sub-Tenon's anesthesia for cataract surgery increased the duration of sensory anesthesia, ocular akinesia, and the duration of analgesia.

Keywords Akinesia · Analgesia · Clonidine · Sub-Tenon's anesthesia

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Introduction

Cataract surgery is the most commonly performed type of ophthalmic surgery. This procedure is commonly performed by phacoemulsification, which requires a small incision [1, 2]. Thus, less invasive anesthetic techniques such as regional [3, 4] and topical anesthesia [5] have been attracting increasing attention.

Sub-Tenon's (episcleral) anesthesia was introduced into clinical practice in the 1990s and was deemed a simple, safe, and effective technique [4, 5]. In 2008, an interview-based study performed by the British Ophthalmic Anaesthesia Society demonstrated that 87.8 % of its interviewed members performed sub-Tenon's block as a routine procedure [6].

Clonidine is an α_2-adrenergic receptor agonist frequently used as an adjuvant to local anesthetics. Although it was originally used as an antihypertensive drug, analgesic properties were observed when the drug was administered into the epidural and intrathecal spaces [7, 8]. Similarly, clonidine improves and prolongs the duration of anesthesia in peripheral blocks [7, 9, 10]. The addition of clonidine to local anesthetics enhanced both akinesia and analgesia in retro- and peribulbar blocks [11–16]. However, as far as we know no study has assessed the effect of clonidine on the quality of sub-Tenon's anesthesia. Therefore, in the present study we hypothesized that the addition of clonidine to 2 % lidocaine could increase the

duration of sensory anesthesia and ocular akinesia of sub-Tenon's anesthesia in patients undergoing cataract surgery. As a secondary endpoint, we evaluated the duration of analgesia i.e., the time until first use of analgesics in the postoperative period.

Methods

After obtaining institutional review board approval and written informed consent forms were signed, a prospective, randomized, double-blind study was performed with 40 patients of both genders. The patients were American Society of Anesthesiologists (ASA) physical status I or II, who were scheduled to undergo cataract surgery by phacoemulsification. Patients were excluded if they had difficulty communicating, were anxious, or were allergic to any medication to be used; had uncontrolled arterial hypertension; had experienced a recent myocardial infarction; were receiving chronic treatment with clonidine; had glaucoma; had previously undergone surgery in the same eye; or had coagulation disorders.

Patients were randomized by computer-assisted, randomized treatment assignments in sequentially ordered and sealed envelopes into two groups of sub-Tenon's anesthesia. The patients of group L ($N = 20$) received 6 ml of 2 % lidocaine plus 1 ml of 0.9 % saline. The patients of group C ($N = 20$) received 6 ml of 2 % lidocaine associated with clonidine 1 μg/kg plus 1 ml of 0.9 % saline. Hyaluronidase (25 IU/ml) was added in both groups. The anesthetic solutions for both groups were prepared by one of the researchers, who did not participate in the performance of the block or assessment of the patients in the perioperative and postoperative period. The subjects were blinded to the sub-Tenon's medication administered.

No premedication was given before the patient arrived in the operation room. No sedative premedication was given and an intravenous catheter (22G) was inserted into a peripheral vein in the operating room. The patients were monitored with electrocardiogram, non-invasive blood pressure, and pulse oximetry. Mean arterial pressure (MAP), heart rate (HR), and pulse oximetry (SpO_2) were recorded every 5 min during the perioperative period and every 15 min during the postoperative period until the patient was discharged. A decrease in MAP exceeding 20 % of the pre-anesthetic value was treated with a IV ephedrine bolus (5 mg), a decrease in HR to a value below 50 beats per min was treated with a IV atropine bolus (0.25 mg), and supplemental oxygen was administered by nasal cannula for hypoxemia ($SpO_2 < 90$ %).

The same anesthesiologist, who was blinded to the actual content of the anesthetic solution used, performed all blocks. The conjunctiva and cornea were anesthetized with two drops of 0.5 % proxymetacaine chlorhydrate, and antisepsis was performed using drops of iodine in water solution. Sub-Tenon's (episcleral) anesthesia was performed at the medial canthus using a 20G × 1.25 in. intravenous catheter (Jelco Plus, Medex Medical Ltd., Ascot, UK) [17, 18], by a modification of the technique described by Ripart et al. [19]. With the eye in a neutral gaze position, 0.1–0.2 ml of diluted local anesthetic solution was injected using a hypodermic needle (0.4 mm × 13 mm; Becton–Dickinson, Curitiba, Brazil) with the bevel turned toward the globe in the conjunctiva between the bulb and the semilunar fold to induce analgesia and dissect the Tenon's capsule. Subsequently, the tip of the needle of the intravenous catheter was inserted in the conjunctiva between the semilunar fold and the glove and then raised by anterior infiltration to a depth of less than 1 mm, with the bevel of the needle turned tangentially toward the globe. The catheter was displaced slightly medially, thus detaching the globe from the semilunar fold and caruncle, which resulted in a medial gaze position. The catheter was then advanced in the anterior–posterior direction, whereas the bulb was displaced slightly in the medial direction until a loss of resistance was noted at an average depth of 10–15 mm. Thereafter, the needle was removed, and the catheter was advanced posteriorly into the episcleral space. After negative aspiration, the anesthetic solution was slowly injected over the course of 30–60 s. The globe was massaged gently for 5 min to reduce the intraocular pressure and the degree of chemosis. One to 2 drops of tropicamide 0.5 % and cyclopentolate hydrochloride 1.0 % were used for pupillary dilation.

Gender, age, weight, ASA physical status, volume of local anesthetic, and surgical time were noted. Patients were assessed regarding sensory anesthesia (tactile feelings), akinesia of ocular rectus muscles (extrinsic), orbicularis oculi muscle, and levator palpebrae superioris muscle at 1 min (M1), 4 min (M4), and 8 min (M8) after the end of the local anesthetic injection and until the block was deemed sufficient for surgery. Patients were also evaluated every 15 min after the end of surgery until the full regression of the block. Sensory anesthesia was assessed by touching the palpebral area and cornea with a cotton swab as follows: 0 = lack of perception, 1 = partial perception, and 2 = normal perception in the tested area. To assess muscle akinesia, we used the score described by Dempsey et al. [20] and other authors [18, 21]. The ocular rectus muscles were assessed in the superior, inferior, medial, and lateral directions as follows: 0 = no motion, 1 = decreased motion, and 2 = normal motion; the maximum possible score was 8. The motility of levator palpebrae superioris muscle and the orbicularis oculi muscle was assessed by asking the patient to open and close the lids as tightly as possible. The same scoring system

mentioned above was applied with a maximum score of 2 per muscle. Adding the motility scores of the four rectus muscles, levator palpebrae superioris muscle, and the orbicularis oculi muscle resulted in a total maximum score of 12 (total akinesia score), which indicated normal eye motility, whereas a score of 0 indicated total akinesia. Akinesia scores ≤ 3 indicated eligibility for surgery [21]. The duration of sensory anesthesia and akinesia of ocular rectus, levator palpebrae superioris, and orbicularis oculi muscles was defined as the interval between completion of the local anesthetic injection and full recovery of the sensitivity and motion of the specific muscle.

The intensity of pain was assessed using a numeric rating scale, in which 0 = no pain and 10 = worst pain. Pain was classified as mild ($\leq$3), moderate (4–6), or severe (7–10) according to the score obtained. Pain was assessed during puncture and injection of the local anesthetic as well as during the peri- and postoperative periods (30 min and 1, 2, 3, 4, 6, and 24 h). Patients were encouraged to report pain at any moment up to 24 h after surgery. The duration of analgesia was assessed as the interval between the local anesthetic injection and the first request for analgesia by the patient. The timing and number of analgesic doses used in 24 h were also recorded. For this purpose, metamizol 1 g (mild pain), ketoprofen 100 mg (moderate pain), or ketorolac 30 mg (severe pain) was administered intravenously. Adverse effects, perioperative and postoperative complications were also recorded.

The sample size calculation was based on a previous study [13] that detected a difference of 40 min on the duration of ocular akinesia between the patients receiving peribulbar clonidine associated with local anesthetic and those who received only local anesthetic (control group) with a standard deviation of 40 min. Considering these data, 17 patients were needed in each group with a 90 % power and a type I error of 0.05. Because of the possibility of loss of patients during the study, 20 patients were allocated in each group. Comparisons between groups according to age, weight, volume of local anesthetic, surgical time, duration of sensory anesthesia and akinesia of the levator palpebrae superioris, orbicularis oculi and rectus eye muscles were performed using Student's *t*-test. Gender, ASA physical status and number of patients requiring analgesics were analyzed by χ^2 test or Fisher's test when indicated. Eye muscle assessment was performed by Mann–Whitney test or Friedman test followed by the Dunn post hoc test. Kaplan–Meier survival analysis was used to evaluate the duration of analgesia on the postoperative period. Statistical Package for the Social Sciences (SPSS) version 19.0 (SPSS. Inc., Chicago, IL) was used for statistical analysis. A value of $p < 0.05$ was considered as statistically significant.

Results

There were no differences between the groups in age, gender, weight, ASA physical status, total volume of injected local anesthetic and duration of surgery (Table 1). Regarding the total akinesia score (rectus eye muscles, levator palpebrae superioris and orbicularis oculi muscles), clonidine did not reduce the onset of a satisfactory blockade (score $\leq$ 3) (Table 2).

The duration of sensory anesthesia and akinesia of the rectus eye muscles, levator palpebrae superioris, and orbicularis oculi were significantly longer in group C than group L ($p = 0.001$) (Table 3). A post hoc power calculation using the differences on rectus eye muscles akinesia between the groups L and C, and a type 1 error of 0.01 showed that the present study had a statistical power of 95 %. The number of patients that reported pain in the postoperative period (group L = 8 vs group C = 7) was not statistically different between the groups. However, the duration of analgesia was significantly longer in group C than in the group L (Fig. 1; $p = 0.017$). Only two patients in group L reported moderate pain (score of 4–6) and required more than one type of analgesic (metamizol and ketoprofen).

Table 1 Demographic data, volume of local anesthetic, and surgical data

Variable	Group L ($N = 20$)	Group C ($N = 20$)	*p*
Age (years)	68.9 ± 9.9	69.5 ± 8.0	0.839[a]
Weight (kg)	64.7 ± 7.9	68.9 ± 10.0	0.152[a]
Volume of local anesthetic (ml)	6.9 ± 0.3	6.6 ± 0.7	0.190[a]
Surgery time (min)	18.6 ± 6.3	20.6 ± 5.4	0.203[a]
Gender			
Male	7 (35 %)	10 (50 %)	0.337[b]
Female	13 (65 %)	10 (50 %)	
ASA			
I	6 (30 %)	7 (35 %)	0.735[b]
II	14 (70 %)	13 (65 %)	

Values are means and SD, or numbers (%)

[a] Student's *t*-test

[b] χ^2 test

Table 2 Total akinesia score (rectus eye muscles, levator palpebrae superioris, and orbicularis oculi) over time

Time (min)	Group L ($N = 20$)	Group C ($N = 20$)	p^a
M1	4 (0–8)	3 (0–6)	0.063
M4	0.5 (0–3)	0 (0–3)	0.291
M8	0 (0–3)	0 (0–2)	1.000
p^b	0.001	0.001	

Values are medians (range). Satisfactory block score ≤3

[a] Mann–Whitney test

[b] Friedman test

Table 3 Duration of sensory anesthesia and akinesia of the levator palpebrae superioris, orbicularis oculi and rectus eye muscles

Variable	Group L	Group C	p
Sensory anesthesia (min)	114.5 ± 32.2	186.8 ± 51.2	0.001[a]
Akinesia of levator palpebrae superioris (min)	109.3 ± 34.1	177.7 ± 64.1	0.001[a]
Akinesia of orbicularis oculi (min)	87.5 ± 33.5	154.5 ± 61.6	0.001[a]
Akinesia of rectus eye muscles (min)	135.8 ± 36.9	242.6 ± 37.9	0.001[a]

Values are means and SD

[a] Student's t test

No patient reported pain during insertion of the cannula, and during the injection of the local anesthetic. The incidence of chemosis was similar between the groups (40 % in group L vs 35 % in group C). Chemosis associated with subconjunctival hemorrhage occurred in one patient in group L (5 %) and three patients in group C (15 %) ($p > 0.05$). Dry mouth was observed in 15 and 5 %, respectively, of the patients in group L and group C.

Discussion

Several studies revealed that the addition of clonidine to local anesthetic prolongs the duration of the motor block and analgesia [7, 9, 10]. Although the benefit of adding clonidine to a local anesthetic in peripheral blockade is not yet fully established [10], the results of our study showed that clonidine prolongs sensory anesthesia, duration of analgesia and motor block when added to 2 % lidocaine in sub-Tenon's block for cataract surgery. In this regard, clonidine appears to act directly by inhibiting the action potential of Aδ and C fibers and indirectly via pharmacokinetic mechanisms that reduce the vascular removal of local anesthetics surrounding neural structures [7, 22].

It is noteworthy to mention the significant longer durations of sensory anesthesia and ocular akinesia obtained in

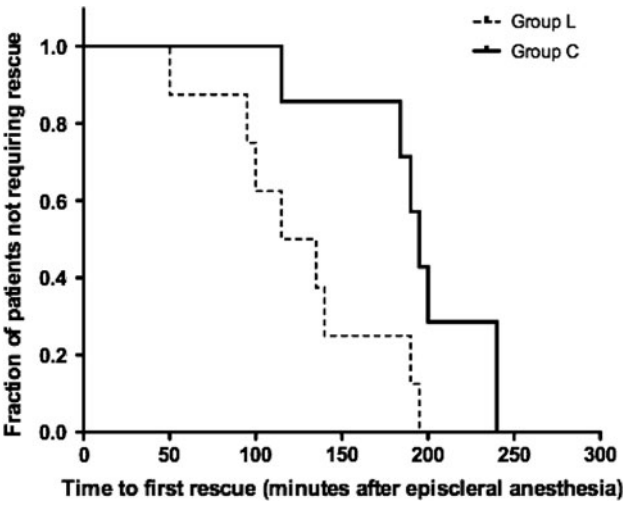

Fig. 1 Kaplan–Meier curves in the patients that used analgesic in the postoperative period. The comparison between curves was performed by log-rank (Mantel-Cox) test ($p = 0.017$)

the presence of clonidine. In fact, several studies reported that the addition of clonidine to local anesthetics provides longer blockade in ophthalmic surgery. However, the duration of sensory anesthesia and ocular akinesia using 1 [12, 13] or 1.5 μg/kg of clonidine [15] for peribulbar block differ from the values reported in the present study. In previous reports, the duration was reported as 77 [12], 78.8 [13], and 83.4 min [15], whereas in the present study the duration of sensory anesthesia was about 180 min. Similarly, the duration of ocular akinesia in the aforementioned studies was reported as 198 [12], 201.2 [13], and 205.8 min [15], respectively, whereas in the present study, this value was about 240 min. In the above studies, the patients reported pain during the peri- [12] and postoperative [12, 13] periods and the pain was more intense in the control group [12]. The time to the first request for analgesics in the clonidine group was significantly longer, and the use of analgesics was lower than in the control group [12, 13]. In contrast, when a higher dose of clonidine was used (2 μg/kg) during a retrobulbar block in cataract surgery, the ocular akinesia lasted 80 min [11].

In the present study, the patients did not report pain during the puncture, the injection of local anesthetic, or surgery. Group L exhibited excellent surgical conditions that were comparable to those obtained with group C, demonstrating the efficacy of sub-Tenon's anesthesia. In fact, pain was only reported during the immediate postoperative period (up to 4 h). It is possible that this divergence regarding the literature is explained by factors associated with both the anesthetic and surgical techniques. The anesthetic technique used in the present study is only minimally invasive and does not require an incision, and it is performed under appropriate conjunctiva analgesia. The cataract was removed by phacoemulsification using a small

incision with only limited manipulation of the ocular structures, which resulted in less pain stimulation and short surgical time. Another factor that might have contributed to the success of blockade was the large volume of local anesthetic employed in the present study (Table 1) compared to that reported in the literature. Small volumes of injected anesthetics promote good analgesia levels but with partial akinesia; however, for full akinesia larger volumes of anesthetics are necessary [3, 23].

Clonidine affects arterial pressure by acting on several points of the central nervous system and spinal cord as well as at the peripheral level. Imidazoline receptors also participate in the hypotensive effects of clonidine [7, 24]. In the present study, no patient exhibited hypotension or bradycardia. This suggests that the action of clonidine is mainly local at the dose used for a sub-Tenon block. The α_2 adrenergic receptor has minimal involvement in ventilation, with no significant effects on hypercapnia or hypoxia [7, 24]. In the present study, hypoxia did not occur in any group. Reduced salivary secretion due to the stimulation of α_2 receptors can cause dry mouth [24]. However, in the present study, this symptom was more evident in group L (15 %) than in group C (5 %). It is possible that this difference was due to the eye drops used to dilate the pupils. Among the ophthalmic solutions used, tropicamide and 1 % cyclopentolate chlorhydrate (cycloplegic) are anticholinergic agents that can result in dry mouth.

This study has some limitations. We evaluated only patients that underwent cataract surgery and we did not include procedures of longer duration and greater intensity of pain. In fact, several studies revealed that cataract surgery performed by phacoemulsification is associated with a lower incidence of pain [5]. Few studies have assessed the effects of clonidine as an adjuvant to local anesthetics in retinal surgery, which is characterized by a longer and more painful procedure. One study reported that the degree of analgesia was appropriate in 85 % of patients with the addition of 1 μg/kg clonidine to 14.5 ml of a mixture of 2 % lidocaine and 0.5 % bupivacaine in the peribulbar block [14]. In another study, 10 % of the patients reported perioperative pain, particularly at the end of the surgery, and 60 % reported pain during the postoperative period with the addition of 0.5 μg/kg of clonidine to a mixture of 4.5 ml of 2 % lidocaine and 0.5 % bupivacaine in the retrobulbar block [16]. It seems that the short duration of surgery in the present study contributed to the satisfactory results observed in both groups. However, we cannot exclude that the addition of clonidine in sub-Tenon's anesthesia might be useful in other surgical procedures that last longer and are associated with higher intensity of pain during the peri- and postoperative period. Thus, further studies are required to assess the combination of clonidine and local anesthetics for sub-Tenon's anesthesia in surgical procedures other than phacoemulsification, such as vitrectomy.

In conclusion, the addition of clonidine 1 μg/kg to 2 % lidocaine in cataract surgery prolonged the duration of sensory anesthesia, ocular akinesia, and the time to the first request for analgesics in the postoperative period, with few adverse effects.

References

1. Eke T, Thompson JR. Safety of local anaesthesia for cataract surgery: why we should look again. Eye. 2003;17:127–8.
2. Malik A, Fletcher EC, Chong V, Dasan J. Local anesthesia for cataract surgery. J Cataract Refract Surg. 2010;36:133–52.
3. Ripart J, Lefrant JY, Vivien B, Charavel P, Fabbro-Peray P, Jaussauf A, Dupeyron G, Eledjam JJ. Ophthalmic regional anesthesia: medial canthus episcleral (sub-Tenon) anesthesia is more efficient than peribulbar anesthesia: a double-blind randomized study. Anesthesiology. 2000;92:1278–85.
4. Guise P. Sub-Tenon's anesthesia: a prospective study of 6000 blocks. Anesthesiology. 2003;98:964–8.
5. Davison M, Padroni S, Bunce C, Rüschen H. Sub-Tenon's anaesthesia versus topical anaesthesia for cataract surgery. Cochrane Database Syst Rev. 2007; 18: CD006291.
6. Vohra SB, Murray PI. Sub-Tenon's block: a national United Kingdom survey. Ophthalmic Surg Lasers Imaging. 2008;393: 79–85.
7. Eisenach JC, De Kock M, Klimscha W. α2-Adrenergic agonists for regional anesthesia: a clinical review of clonidine (1984–1995). Anesthesiology. 1996;85:655–74.
8. Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. Reg Anesth Pain Med. 2008;33:159–67.
9. McCartney CJ, Duggan E, Apatu E. Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. Reg Anesth Pain Med. 2007; 32:330–8.
10. Pöpping DM, Elia N, Marret E, Wenk E, Tramèr MR. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks. Anesthesiology. 2009;111:406–15.
11. Mjahed K, Harrar N, Hamdani M, Amraoui M, Benaguida M. Lidocaine–clonidine retrobulbar block for cataract surgery in the elderly. Reg Anesth. 1996;21:569–75.
12. Madan R, Bharti N, Shende D, Khokhar SK, Kaul HL. A dose response study of clonidine with local anesthetic mixture for peribulbar block: a comparison of three doses. Anesth Analg. 2001;93:1593–7.
13. Bharti N, Madan R, Kaul HL, Khokhar SK, Mishra S. Effect of addition of clonidine to local anaesthetic mixture for peribulbar block. Anaesth Intensive Care. 2002;30:438–41.
14. Calenda E, Quintyn JC, Brasseur G. Peribulbar anaesthesia using a combination of lidocaine, bupivacaine and clonidine in vitreoretinal surgery. Indian J Ophthalmol. 2002;50:205–8.
15. Eldeen HM, Faheem MR, Sameer D, Shouman A. Use of clonidine in peribulbar block in patients undergoing cataract surgery. Aust J Basic Appl Sci. 2011;5:247–50.
16. Yazbeck-Karam V, Siddik-Sayyid SM, Abi Nader EL, Barakat DE, Karam HS, Cherfane GM, Hajj Hussein JN, Aouad MT. Supplementation of retrobulbar block with clonidine in vitreoretinal surgery: effect on postoperative pain. J Clin Anesth. 2011;23:393–7.

17. Kumar CM, Dodds C. A disposable plastic sub-Tenon cannula. Anaesthesia. 2001;56:399–400.
18. Mather CM. Comparison of i.v. cannula and Stevens' cannula for sub-Tenon's block. Br J Anaesth. 2007;99:421–4.
19. Ripart J, Metge L, Prat-Pradal D, Lopez FM, Eledjam JJ. Medial canthus single-injection episcleral (sub-Tenon's anesthesia): computed tomography imaging. Anesth Analg. 1998;87:42–5.
20. Dempsey GA, Barrett PJ, Kirby IJ. Hyaluronidase and peribulbar block. Br J Anaesth. 1997;78:671–4.
21. Frow MW, Miranda-Caraballo JI, Akhtar TM, Hugkulstone CE. Single injection peribulbar anaesthesia. Total upper eyelid drops as an end-point marker. Anaesthesia. 2000;55:750–6.
22. Kopacz DJ, Bernards CM. Effect of clonidine on lidocaine clearance in vivo. A microdialysis study in humans. Anesthesiology. 2001;95:1371–6.
23. Li HK, Abouleish A, Grady J, Groeschel W, Gill KS. Sub-Tenon's injection for local anesthesia in posterior segment surgery. Ophthalmology. 2000;107:41–6.
24. Khan ZP, Ferguson CN, Jones RM. Alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. Anaesthesia. 1999;54:146–65.