

Effects of tizanidine premedication on the duration of perioperative maintenance dose of vecuronium bromide

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ABSTRACT

Aim. The aim of this study was to evaluate the effects of preoperative administration of tizanidine on the maintenance dose duration of the nondepolarizing muscle relaxant, i.e. vecuronium bromide.

Material and Methods. This prospective clinical study was conducted in 30 adult male patients scheduled for elective inguinal hernia surgery. Patients were categorised into two randomised groups based on the premedication use. Group 1 included patients ($n = 15$) who received oral diazepam (Diazem) in the evening prior to the surgery, as well as meperidine (*Dolantin*) 1 mg/kg^{-1} (max. 50 mg) i.m. with 50 ml water by mouth 1 hour before the procedure. Group 2 comprised patients ($n = 15$) who were given oral tizanidine 4 mg in the evening before the surgery, as well as oral tizanidine 4 mg with 50 ml water 1 hour prior to the operation. The following parameters were recorded in both groups: pre-operative and perioperative diastolic arterial blood pressure, systolic arterial blood pressure, mean arterial blood pressure, heart rate, respiratory rate, pre-operative vecuronium bromide maintenance doses, procedure time and postoperative score according to the Ramsay scale in 1st, 2nd and 3rd hour.

Results. No significant difference was observed between the two groups with regard to the pre-operative and perioperative haemodynamic variables and the respiratory rate ($P > 0.05$), although it was found that vecuronium maintenance dose duration was significantly higher in the tizanidine premedicated group ($P = 0.015$). In addition, the operative time ($P = 0.128$) and the postoperative patients' Ramsay scores did not differ statistically between the two groups ($P > 0.05$).

Conclusions. The prolonged duration of vecuronium maintenance dose, the increased nondepolarizing block time, as well as haemodynamic stability preservation in patients undergoing inguinal hernia surgery following preoperative oral administration of tizanidine support the view that tizanidine can be used as an effective and safe myotonolytic premedication agent.

Introduction

Tizanidine, an imidazoline, is also an α_2 receptor agonist mainly derived from centrally acting myo-

tonolytic clonidine. It is characterized by short duration of action, little effect on heart rate and blood pressure, as well as antinociceptive and

anticonvulsant effects [1]. Oral administration of tizanidine is quickly absorbed. It reaches its maximum plasma concentration in 0.75 to 2 hours. Since its elimination half-life is 2.1 to 4.2 hours, it may be applicable even in the day care surgery [2,3]. The use of α_2 -adrenergic agonists for the treatment of muscle spasticity is well known [4–6]. Tizanidine is a short-acting and potent agent which effectively reduces spasticity caused by multiple sclerosis, acquired brain injury or spinal cord injury [7,8]. The most frequently reported adverse effects include dryness of the mouth, drowsiness, dizziness and fatigue, although it is generally a well tolerated agent. It has been shown that tizanidine has a similar clinical efficacy as baclofen and diazepam [9,10]. Additionally, fewer treatment interruptions due to adverse events were also observed [11]. Tizanidine, which shows muscle relaxant, sedative and anxiolytic properties, is also used in the treatment of musculoskeletal pain [6]. However, the role of tizanidine in the treatment of postoperative pain was investigated [12]. The use of tizanidine was supported in pain management studies, which included myofascial pain, neuropathic pain, chronic daily headache and low back pain [13–17]. Furthermore, tizanidine demonstrated fewer cardiovascular side effects, thus, making it an appealing drug to be used in anaesthesia [18]. There are several studies assessing the role of tizanidine as an effective anaesthetic premedication. In fact, oral premedication with tizanidine alleviates the hypertensive response during laryngoscopy, as well as reduces the induction dose of midazolam, the maintenance dose of propofol, and the minimum alveolar concentration of sevoflurane. Additionally, it prolongs spinal anaesthesia and reduces isoflurane consumption [1,19–22]. Although tizanidine, which proved effective in spastic patients, was reported as a premedication in various studies, the findings with regard to its use with nondepolarizing drugs are scarce. Therefore, this study aimed to assess the effect of tizanidine premedication on the maintenance dose of vecuronium bromide, which is a neuromuscular blocking agent.

Materials and Method

30 male patients who were eligible for elective inguinal hernia surgery under general anaesthesia

were included in this study. Patients were aged between 18–60 years and were assessed according to the American Society of Anesthesiologists Classification (ASA) 1, 2 and 3. Individuals with uncontrolled diabetes or hypertension, a history of cardiorespiratory, renal, endocrine, hepatic, neurological and psychiatric disorders, and those exposed to α_2 adrenergic agonists in the preceding two weeks were excluded from the study. Prior to the surgery, the patients were provided with a complete description of the study, and subsequently, an informed consent was obtained from each participant. Taksim Research and Training Hospital Local Ethical Committee approved the presented study.

Following the pre-anaesthetic examination, an 8-hour fast was recommended before the surgery. All patients were evaluated the night before the planned operation, and a full physical examination was performed. After brief information was given to the patients about the surgery, they were informed about the drugs used before the surgery, the anaesthesia method applied in the operating room and the TOF-Guard device (Biometer, Denmark). Patients were then divided into two randomised groups on the basis of the premedication use. Group 1 comprised patients ($n = 15$) who had received oral diazepam (Diazem) the evening before the operation and meperidine (Dolantin) 1 mg/kg^{-1} (max 50 mg) i.m. + 50 ml water per os 1 hour pre-operatively; Group 2 included patients ($n = 15$) who had oral tizanidine 4 mg administered in the evening before the operation and oral Tizanidine 4 mg + 50 ml water 1 hour pre-operatively. In addition, atropine 0.5 mg i.m. was administered to both groups as a standard measure. Preoperatively, arterial systolic blood pressure (SABP), arterial diastolic blood pressure (DABP), and mean arterial blood pressure (MABP), respiratory rates (RR), and heart rate (HR) values were recorded 3 minutes before the induction of general anaesthesia. The electrodes of the TOF-Guard device were placed on the ulnar nerve and the mechanical sensor was placed on the medial side of the patient's thumb and secured. Neuromuscular monitoring was undertaken using a Kontron Minimon (Kontron Instruments, Model Minimon, 7137 Plus, Charter Kontron, England) in the operating room. Following the intravenous administration of 1 mcg/kg^{-1} fentanyl (maximum 75 mcg/kg^{-1}), thiopental (Pentothal) 7 mg/kg^{-1} (maximum 500

mg) was administered and the TOF-Guard device was calibrated to 100%. Subsequently, muscle relaxation was induced with vecuronium bromide (Norcuron) 0.1 mg/kg⁻¹, the patient was intubated and delivered to the surgical team. All patients were operated by the same surgical team blinded to the medications involved in the study. Vital signs and sedation were assessed and recorded according to the Ramsay Scale (RSS). Maintenance of anaesthesia was facilitated using an inhaled mixture 65% N₂O-35% O₂ and isoflurane (Forane) 0.5–1%. During the operation, no other analgesic was administered. The depth of anaesthesia was provided with volatile anaesthetic dose changes according to the following vital signs, SABP, DABP, MABP, RR and HR, which had been recorded every 5 minutes pre-operatively. When the 3rd response of TOF was observed in the TOF-Guard device, the patients' muscle relaxant requirements were maintained using doses of 30 mcg/kg⁻¹ in each patient. After the surgical team completed the procedure, the volatile, anaesthetic and N₂O gases were turned off and the patient's ventilation continued with the breathing circuit O₂. Each patient received 0.5 mg of atropine i.v. When the 3rd response was observed in the TOF-Guard device, neostigmine methyl sulfate (neostigmine) was administered i.v. for decurarization (1.5 mg). When the TOF response was 65% according to the

TOF-Guard device, the patient was extubated. The patients were transferred to the recovery room and monitored for one hour. The sedation status of the patients was evaluated with a 6-stage Ramsay scale. According to the Ramsay scale, the scoring levels are the following: (1) Irritable, agitated and/or restless patient; (2) cooperative, oriented and calm; (3) only obeying orders; (4) sleeping, although responding immediately to glabella tapping or loud noise; (5) sleeping, with a slow response to tapping the glabella or loud noise; (6) no response at all to these stimuli. Our patients were evaluated with the Ramsay sedation score in the 1st, 2nd and 3rd postoperative hours.

Statistical Analysis

Statistical analyses were performed with the SPSS Version 18.0 (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test for continuous variables was used to evaluate differences between groups. Fisher's Exact and χ^2 tests were applied to analyse differences in proportions. A *P*-value of *P* ≤ 0.05, was defined as statistically significant.

Results

When the ASA results of the patients were evaluated, 11 patients in Group 1 presented ASA score

Table 1. Comparison of clinical variables between the two groups

Variable (Mean ± SD)	Group 1 (n = 15)	Group 2 (n = 15)	Combined 1 & 2 (n = 30)	<i>P</i> Value
Age	49.87 ± 13.15	46.07 ± 15.94	47.97 ± 14.49	0.482
Weight	74.13 ± 7.5	71.07 ± 6.83	72.6 ± 7.22	0.252
Pre-op SABP	133 ± 18.11	134.33 ± 21.12	133.67 ± 19.34	0.854
Pre-op DABP	81.67 ± 11.13	84.47 ± 13.15	83.07 ± 12.05	0.534
Pre-op MABP	111 ± 14.93	107.80 ± 17.05	109.43 ± 15.83	0.581
Pre-op HR	79.47 ± 12.79	73.93 ± 5.71	75.93 ± 11.27	0.137
Pre-op RR	16.73 ± 2.74	16.87 ± 1.46	16.80 ± 2.16	0.869
Periop SABP	147.40 ± 16.19	141.80 ± 25.35	144.60 ± 27.09	0.477
Periop DABP	86.40 ± 11.43	82.13 ± 10.96	84.27 ± 11.21	0.306
Periop MABP	113.93 ± 14.82	107.60 ± 14.19	110.77 ± 14.61	0.240
Periop HR	79.60 ± 9.95	72.27 ± 11.64	76.70 ± 10.13	0.074
Periop RR	17.60 ± 3.64	16.80 ± 2.68	17.20 ± 3.17	0.499
Vec Int	35.53 ± 8.75	42.93 ± 6.75	39.23 ± 8.56	0.015*
Op Time	73.80 ± 20.28	85.53 ± 20.68	79.67 ± 20.99	0.128

Pre-op SABP: Pre-operative Systolic Arterial Blood Pressure; Pre-op DABP: Pre-operative Diastolic Arterial Blood Pressure; Pre-op MABP: Pre-operative Mean Arterial Blood Pressure; Pre-op HR: Pre-operative Peak Heart Rate; Pre-op RR: Pre-operative Respiratory Rates; Periop SABP: Peri-operative Systolic Arterial Blood Pressure; Periop DABP: Peri-operative Diastolic Arterial Blood Pressure; Periop MABP: Peri-operative Mean Arterial Blood Pressure; Periop HR: Peri-operative Peak Heart Rate; Periop RR: Peri-operative Respiratory Rates; Vec Int: Vecuronium maintenance dosage Interval; Op Time: Operation Time; *P*-values were calculated using Pearson χ^2 test; Level of significance set at *P* ≤ 0.05

Table 2. Comparison of postoperative Ramsay sedation scores between the two groups

Time	Ramsay Score	Group 1		Group 2		P Value
		n	%	n	%	
First Hour	1	-	-	1	6.7	0.560
	2	3	20	5	33.3	
	3	10	66.7	8	53.3	
	4	2	13.3	1	6.7	
Second Hour	2	6	40	11	73.3	0.451
	3	9	60	4	26.7	
Third Hour	2	13	86.3	15	100	0.143
	3	2	13.7	-	-	

N: number of patients; %: percentage of group; P-values were calculated using Pearson χ^2 test; Level of significance set at $P \leq 0.05$

of I, three presented ASA II and one presented ASA III score; in Group 2, 9 patients showed ASA I score, and six - ASA II score. No significant differences were observed between the two groups ($P = 0.332$). There was also no statistically significant difference between the groups in terms of age ($P = 0.482$) and weight ($P = 0.252$). **Table 1** shows the statistical comparisons of haemodynamic variables, heart rates and respiratory rates between the two groups, pre-operatively and perioperatively. It was determined that the duration of the vecuronium maintenance dose was significantly prolonged in the tizanidine premedicated group ($P = 0.015$). However, the procedure time did not statistically differ between the two groups ($P = 0.128$). The comparison of the Ramsay sedation scores of the patients recorded at the first hour, second hour and third hour post-operatively are presented in **Table 2**. There were no significant differences in Ramsay sedation scores between the two groups, ($P > 0.05$).

Discussion

Methyldopa, an analogue of levodopa, enters the norepinephrine synthesis pathway and is converted to α -methylnorepinephrine and α -methylepinephrine. These pseudotransmitters activate α -adrenoceptors, in particular central α_2 receptors. As a result, norepinephrine is released and sympathetic tone decreases. Sympathetic tone is also reduced in patients receiving tizanidine, an α_2 agonist, due to the fact that the transmitters at the junctions in the spinal cord are adrenergic. Furthermore, studies in animal models also showed that tizanidine inhibits both mono- and poly-synaptic reflexes [6,23].

However, unlike baclofen, it reduces both mono- and poly-synaptic excitation, although primarily monosynaptic excitations [6,24]. Some researchers suggest that tizanidine inhibits polysynaptic reflexes [6,25]. The result of this study might be accounted for by a decrease in the tone-providing impulse to the adductor pollicis. Tizanidine, which has a central α_2 noradrenergic agonist effect, decreases norepinephrine release and causes a decrease in the sympathetic tone, which initially might suggest that it potentiates muscle relaxation. However, the working principle of the TOF-Guard device in the study is supra-maximal quadruple stimulus given at 10–12 second intervals, leading to severe muscle twitch of the adductor pollicis. Therefore, the decrease in tone in the muscle proximal to the electrodes could not be assessed due to the working principle of the device. The working mechanism of TOF-Guard device is designed according to the “all or nothing” principle of muscle contraction. If the TOF-Guard device could provide submaximal stimulation instead of supramaximal stimulation, the decrease in muscle tone would be significant. Moreover, submaximal stimulation could require impulses from the spinal cord providing the tone for muscle contraction.

Tizanidine, an imidazolidine derivative, is an effective alternative to oral clonidine [18]. In fact, the imidazolidine compounds related to clonidine and tizanidine are thought to inhibit acetylcholine transmitter release [26]. A study in this area using rabbit distal colon evaluated the potential effects on isotonic contraction. Extrinsic pelvic parasympathetic nerves were stimulated for 30 seconds at a frequency of 2 Hz. Atropine, when added to the medium, abolished the contractions induced by acetylcholine, but only partially

reduced the responses to the nerve stimulation. Clonidine and the related compounds (UK 14819, UK 14304, UK 15121, UK 11957 and UK 42620) inhibited nerve stimulation-induced contractions at concentrations which had no effect on exogenous acetylcholine responses. In our study, the imidazolide Tizanidine [18], which also involves these metabolites, may have played a role in the prolongation of neuromuscular blockade. Since acetylcholine acts as a transmitter in the intestine and at the neuromuscular junction, tizanidine may also have direct effects on the neuromuscular junction [26]. However, to date no evidence is available to substantiate this thesis. During general anaesthesia, clonidine increases intraoperative circulatory stability by lowering catecholamine levels. This includes peripheral nerve blockade during regional anaesthesia. Clonidine prolongs the duration of the block, as it can alter the direct effects on the spinal cord through the postsynaptic α_2 receptors located in the dorsal horn. A reduction of post-operative tremor, inhibition of opioid-induced muscle stiffness, reduction of opioid withdrawal symptoms, and treatment of some chronic pain symptoms are among the areas where it is applicable. Its side effects comprise bradycardia, hypotension, sedation, respiratory depression and dryness of the mouth. Although methyldopa and clonidine are adrenergic agonists, they are also considered sympatholytic, since they reduce sympathetic release [27]. In this study, the effect of the first dose of vecuronium bromide was significantly prolonged in the tizanidine group. There is no known direct drug interaction between vecuronium bromide and tizanidine [27]. Thus, the absence of drug interaction may also indicate that the effect of tizanidine on prolonging neuromuscular block does not occur by binding to post junctional receptors at the neuromuscular junction where vecuronium bromide acts. Nonetheless, tizanidine does seem to prolong the effect of the neuromuscular block when the effects of neuromuscular blocking agents are monitored objectively using the TOF-Guard method. Therefore, there might be a direct action on the ulnar nerve, a peripheral nerve, or on the neuromuscular plate. However, this is unlikely, as the ulnar nerve at that level consists only of myelinated sensory and motor fibres, and the absence of synapses in that area that would require transmitters. Additionally, there is no evi-

dence that tizanidine has a direct effect on the nerves. Since imidazolidine substances related to clonidine are thought to inhibit transmitter release, it might be that they inhibit the release of the stored acetylcholine in the presynaptic vesicles in the neuromuscular plate.

Tizanidine reduces spasticity, possibly by increasing presynaptic inhibition of motor neurones. Tizanidine was shown to have no direct effect on the skeletal muscle fibers or the neuromuscular junction. Although having no major effect on monosynaptic spinal reflexes, it has its main effect on polysynaptic pathways. Consequently, it is thought to decrease the facilitation of spinal motor neurons [3]. Muscle reflexes are particularly depressed (polysynaptic reflexes) by tizanidine, which results in both spinal and supraspinal effects. Nevertheless, the exact mechanism of tizanidine action remains unknown. There are clinical studies evaluating a decrease in blood pressure, sedation and sympatholytic effects caused by tizanidine. In addition, in animal studies, tizanidine was shown to have anticonvulsant effects and to inhibit gastrointestinal motility. Tizanidine may have a gastric protective effect due to its acid inhibitory effect through the nervus vagus with noreadrenergic suppression [28]. In studies investigating the antispastic effect of tizanidine, it was shown that the frequency of spasm and clonus improved significantly. Thus, tizanidine is primarily effective presynaptically [29–31]. In contrast, the depressant effect of tizanidine on interneurone polysynaptic excitation is due to the reduction of their postsynaptic effects rather than the inhibition of their presynaptic release of excitatory transmitters [32]. However, it is unlikely that these effects directly affected the results of our study, where supramaximal stimulation was administered locally and peripherally by the TOF-Guard device. Animal models also showed that tizanidine has a hypothermic effect [33,34]. A decreased oxygen consumption and energy expenditure were observed after a single dose of 6 mg and 12 mg tizanidine in healthy subjects [35]. The reduction in oxygen consumption and energy expenditure, and hence the possibility of hastening hypothermia could, theoretically, be vital, since hypothermia is allowed during neuromuscular blockade. In terms of our use of atropine, which is parasympatholytic, it was thought to have no effect in

our study, as it was administered to both groups. Diazepam shows a muscle relaxant effect, and with 5 mg diazepam given at night, active metabolites may have been present in the course of the study. Nonetheless, a significantly longer duration in the muscle blockade was found in the tizanidine group.

Conclusion

In this study, the effect of oral tizanidine on the duration of vecuronium maintenance dose in general anaesthesia was investigated. It was shown that pre-operative tizanidine increased the duration of vecuronium maintenance doses more significantly than placebo. Haemodynamic changes in both groups were not significant. Thus, it is suggested that various doses of tizanidine and various times of prescription prior to operation should be studied. In conclusion, more evidence is needed on the concomitant use of tizanidine and neuromuscular nondepolarizing blockers.

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Conflict of interest statement

The authors declare no conflict of interest.

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References

1. Coward DM. Tizanidine: neuropharmacology and mechanism of action. *Neurology*. 1994;44:6–10. PMID: 7970012.
2. Henney HR, Runyan JD. A clinically relevant review of tizanidine hydrochloride dose relationships to pharmacokinetics, drug safety and effectiveness in healthy subjects and patients. *Int J Clin Pract*. 2008;62(2):314–24. doi:10.1111/j.1742-1241.2007.01660.x.
3. Wajima Z, Yoshikawa T, Ogura A, Imanaga K, Shiga T, Inoue T. Oral tizanidine, an α_2 -adrenoceptor agonist, reduces the minimum alveolar concentration of sevoflurane in human adults. *Anesth Analg*. 2002;95(2):393–6. doi: 10.1097/00000539-200208000-00028.
4. Nance PW. Alpha adrenergic and serotonergic agents in the treatment of spastic hypertonia. *Phys Med Rehabil Clin N Am* 2001;12(4): 889-905. PMID:11723869.
5. Taricco M, Adone R, Pagliacci C, Telaro E. Pharmacological interventions for spasticity following spinal cord injury. *Cochrane Database Syst Rev* 2000(2):CD001131.doi: 10. 1002 /14651858.CD001131.
6. Wagstaff AJ, Bryson HM. Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs* 1997;53(3): 435-52. doi: 10.2165/00003495-199753030-00007.
7. Nance PW, Bugaresti J, Shellenberger K, Sheremata W, Martinez-Arizala A. Efficacy and safety of tizanidine in the treatment of spasticity in patients with spinal cord injury. *North American Tizanidine Study Group. Neurology* 1994;44 (11 Supply 9): 44-51. PMID:7970010.
8. Paisley S, Beard S, Hunn A, Wight J. Clinical effectiveness of oral treatments for spasticity in multiple sclerosis: a systematic review. *Mult Scler* 2002;8(4):319-29. doi: 10.1191/1352458502ms795rr.
9. Groves L, Shellenberger MK, Davis CS. Tizanidine treatment of spasticity: a meta-analysis of controlled, double-blind, comparative studies with baclofen and diazepam. *Adv Ther* 1998;15 (4):241-51. PMID:10186943.
10. Lataste X, Emre M, Davis C, Groves L. Comparative profile of tizanidine in the management of spasticity. *Neurology* 1994; 44(11 Supply 9): 53-9. PMID:7970011.
11. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. *J Pain Symptom Manage* 2004;28(2):140-75. doi: 10.1016/j.jpainsymman.2004.05.002.
12. Hord AH, Denson DD, Azevedo MI. Systemic tizanidine hydrochloride (zanaflex) partially decreases experimental postoperative pain in rats. *Anesth Analg* 2001; 93(5):1307-9. doi: 10.1097/00000539-200111000-00056.
13. Malanga GA, Gwynn MW, Smith R, Miller D. Tizanidine is effective in the treatment of myofascial pain syndrome. *Pain Physician* 2002;5(4): 422-32. PMID:168821.
14. Manfredini D, Romagnoli M, Cantini E, Bosco M. Efficacy of tizanidine hydrochloride in the treatment of myofascial face pain. *Minerva Med* 2004;95(2):165-71. PMID:15 272252.
15. Semenchuk MR, Sherman S. Effectiveness of tizanidine in neuropathic pain: an open-label study. *J Pain* 2000;1(4): 285-92. doi: 10.1054/jpai.2000.9435.
16. Saper JR, Lake AE 3rd, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002; 42(6):470-82. doi: 10.1046/j.1526-4610.2002.02122.x.
17. Gorska J. Effects of back pain treatment with tizanidine. *Ortop Traumatol Rehabil* 2005;7(3): 306-9. PMID:17611479.
18. Miettinen TJ, Kanto JH, Salonen MA, Scheinin M. The sedative and sympatholytic effects of oral tizanidine in healthy volunteers. *Anesth Analg* 1996;82(4):817-820. doi.org/10.1097/00000539-199604000-00024.
19. Tabari M, Alipour M, Esalati H. Evaluation of oral tizanidine effects on intra operative hemodynamic responses during direct laryngoscopy under general anesthesia. *Iran Red Crescent Med J* 2013;15(7):541-6. doi: 10.5812/ircmj.11540.

20. Takenaka M, Iida H, Kasamatsu M, Katoh H, Tashiro T, Dohi S, Tetsuo I et al. Tizanidine for preanesthetic medication. *Masui* 1996;45(8):971-5. doi: 10.5812/ircmj.11540
21. Sanket B, Samudiyatha TJ, Nethra SS, Kannan S, Nagaraj S. A randomised controlled double blind study to assess the effect of oral tizanidine premedication on intraoperative isoflurane consumption in patients undergoing laparoscopic surgeries under general anaesthesia. *Indian J Clin Anaesth* 2021;8(2):214-20. doi:10.18231/j.ijca.2021.043
22. Omote K, Satoh O, Sonoda H, Kumeta Y, Yamaya K, Namiki A. Effects of oral alpha 2 adrenergic agonists, clonidine and tizanidine, on tetracaine spinal anaesthesia. *Masui* 1995; 44(6):816-23. PMID:7637157.
23. Skoog B. A comparison of the effects of two antispastic drugs, tizanidine and baclofen, on synaptic transmission from muscle spindle afferents to spinal interneurons in cats. *Acta Physiol Scand* 1996;156(1):81-90. doi: 10.1046/j.1365-201X.1996.444159000.x.
24. Davies J. Selective depression of synaptic excitation in cat spinal neurones by baclofen: an iontophoretic study. *Br J Pharmacol* 1981;72(2):373-84. doi: 10.1111/j.1476-5381.1981.tb09137.x.
25. Tanabe M, Kaneko T, Tonohiro T, Iwata N. The pharmacological properties of CS-722, a newly synthesized centrally acting muscle relaxant. *Neuropharmacology* 1992;31(10):1059-66. doi: 10.1016/0028-3908(92)90108-2.
26. Thompson DC, Diamond L, Altieri RJ. Atypical presynaptic alpha-adrenoceptor modulation of neurally-mediated cholinergic responses in guinea-pig tracheal smooth muscle. *Pulm Pharmacol* 1992;5(4):251-5. doi: 10.1016/0952-0600(92)90067-q.
27. Morgan GE, Mikhail MS. *Clinical Anesthesiology* 2nd ed., Appleton/Lange, 1996 :180,155.
28. Maeda-Hagiwara M, Watanabe H, Kanaoka R, Watanabe K. Influence of clonidine and a new related imidazoline derivative (tizanidine) on rat gastric mucosa. *Pharmacology* 1986;32(2):109-13. doi: 10.1159/000138158.
29. Chen DF, Bianchetti M, Wiesendanger M. The adrenergic agonist tizanidine has differential effects on flexor reflexes of intact and spinalized rat. *Neuroscience* 1987; 23(3): 641-7.
30. Matsumiya T, Shimura H, Shibuya T. The effects of Tizanidine on C fiber reflex and heat evoked discharge in the cats. *Pharmacometrics* 1986;31:81-6.
31. Milanov I, Georgiev D. Mechanism of tizanidine action on spasticity. *Acta Neurol Scand* 1994;89(4):274-9. doi: 10.1111/j.1600-0404.1994.tb01680.x.
32. Curtis DR, Leah JD, Peet MJ. Spinal interneurone depression by DS 103-282. *Br J Pharmacol* 1983 79(1); 9-11. doi: 10.1111/j.1476-5381.1983.tb10487.x
33. Kameyama T, Nabeshima T, Yamada S. Hypothermic and antiinflammatory effects of tizanidine. *Pharmacometrics* 1985;30(5): 867-71.
34. Yanagita T, Yamamura H, Igarashi S. Effects of tizanidine in healthy volunteers: double blind study compared with diazepam and a placebo. *Int J Clin Pharmacol Res* 1988;8(2):75-94. PMID:3378856.
35. Taittonen M, Raty H, Kirvela O, Aantaa R, Kanto J. The metabolic effects of oral tizanidine in healthy volunteers. *Acta Anaesthesiol Scand* 1995;39(3):628-32. doi: 10.1111/j.1399-6576.1995.tb04139.x.