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Epidural dexmedetomidine in regional anesthesia to reduce anxiety

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Abbreviations:
Alfa 2 (α 2)
Bispectral index (BIS)
Epidural block(EDB)
Sistolic blood pressure (SBP)
Mean blood pressure (MBP)
Dyastolic blood pressure (DBP)

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SUMMARY

The use of adjuvants in local anesthesia in order to decrease the anxiety is frequently associated to deep sedation, and a consequent respiratory depression. The emergence of alpha 2 agonists, important because of their qualities (sedation, analgesia and amnesia), allows their use by intravenous via during anesthesia. Finding their receptors at the medullar level will give diverse sedation levels when administering them by epidural via, improving anesthesia's quality and decreasing the use of adjuvant intravenous drugs. **Results:** 40 (female and male) patients were included in this study. They were subjected to abdominal and lower members surgery. They were given epidural dexmedetomidine at a dose of 1 μg/kg, plus lidocaine and epinephrine at 3-4 mg/kg. The obtained sedation degree, according to Ramsay, at five minutes was of 3, and it was of 3-4 from 15 to 90 minutes, in the 90% of the population. These frequencies were analyzed through the χ^2, being $p < 0.05$. The patients kept their hemodynamic parameters stable, without respiratory depression.

Key words: Alpha 2 agonists, epidural dexmedetomidine, sedation.

RESUMEN

El uso de adyuvantes en anestesia regional para disminuir la ansiedad, con frecuencia se asocia a sedación profunda y a la consecuente depresión respiratoria. El advenimiento de los alfa 2 agonistas por sus cualidades (sedación, analgesia y amnesia) permiten su uso por vía endovenosa durante la anestesia. Al encontrar receptores a nivel medular de los mismos, permiten obtener diversos grados de sedación, al administrarlos por vía peridural, mejorando la calidad de la anestesia y disminuyendo el uso de adyuvantes endovenosos. ***Resultados:*** *Se incluyeron 40 pacientes, femeninos y masculinos, para cirugía de abdomen y miembros inferiores, a los que se les administró dexmedetomidina peridural 1 μg/kg, más lidocaína con epinefrina a 3-4 mg/kg. El grado de sedación, según Ramsay, obtenido desde los cinco minutos fue de 3, y de los 15 a los 90 minutos en el 90% de la población, de 3-4. Estas frecuencias se analizaron con la χ^2, siendo la $p < 0.05$. Los pacientes mantuvieron estables sus parámetros hemodinámicos, sin depresión respiratoria.*

Palabras clave: *α2 agonistas, dexmedetomidina peridural, sedación.*

INTRODUCTION

Patients who were administered locoregional anesthesia may require adjuvant drugs because various degrees of anxiety are observed during trans-anesthetic period. Such anxiety is caused by the procedure to be performed, unknown operating room area with unknown personnel and due to patient's condition and disease and unrealistic fears commented by non-trained people such as family and friends about the pain and anesthetic risks.

In epidural block procedures there are signs indicating that the anesthesia is installed such as sensory and motor block, hemodynamic effects, peripheral vasodilation, and so on, and yet the patient mentions feeling "pain", which is caused by anxiety. The management of the patient begins by applying adjuvant drugs (e.g. anxiolytics, opioids, etc.) which are sometimes sufficient; however, it may be necessary to increase the doses leading to the potential risk to reach levels of deep sedation and even general anesthesia, whether it is inhaled, intravenous or balanced anesthesia.

The drugs that, by their qualities, can be used as adjuvants in anesthesia include alpha-2-adrenergic agonists (α_2) which provide sedation, anxiolysis, hypnosis, analgesia and sympathycolysis.

Another advantage is that their effects are easily reversible with alpha-2-adrenergic agonists such as atipamazole (with an affinity for the receptors of 60:1, compared to dexmedetomidine), which is the dependent dose, it rapidly reverses the sedation and cardiovascular effects at doses from 15 to 150 μg/kg.

α_2-adrenergic agonists have characteristics that make them valuable to the anesthesia; however, the cardiovascular effects (hypotension and/or bradycardia) appear to be its main disadvantage.

α_2 receptors are distributed both in the central nervous and peripheral system in structures innervated by sympathetic nerve endings and non-nerve cells.

Among the actions that result from its stimulation highlights the inhibition of neurotransmitter release in the presynaptic synapses and decreased inlet flow of the ion signal in postsynapse, these and other intermediate mechanisms causing an range of disparate effects: peripheral vasoconstriction, generalized vasodilatation, decrease in myocardial demands of oxygen and heart rate, cardiac output, increased diuresis, sedation, analgesia, disturbances of salivary and gastrointestinal secretion[1-4].

α_2-adrenergic agonists can produce sedation and analgesia without compromising respiratory function. On the other hand, the hemodynamic effects could be minimized or even be used[4].

New drugs are getting more selective for one type of receptor; dexmedetomidine is a highly selective α_2-adrenoceptor agonist[4].

Sedation is the act of reducing anxiety, stress, excitation and irritability by drug administration, by which anxiolysis, decreased attention, amnesia, maintenance of verbal communication and patient's cooperation are achieved, and physiologically there is an active response to the eyeblink-eliciting ocular stimulus, a reduction in sympathetic activity and possibly in muscle tone. *Active sedation* is characterized by allowing a focused and reactive patient prepared to respond lucidly to the indications.

The elimination half-life of dexmedetomidine is approximately 4 times shorter than that of clonidine, which makes it a more useful drug when most rapid changes are required in the progression of this state, as well as in postoperative sedation and intensive care.

In the intimate mechanism of the sedative, hypnotic, and anxiolytic actions is known to be involved the *locus coeruleus*. It regulates the sleep-wake cycle and is a small nucleus located in the brainstem, it receives and sends in diffuse manner connections through the brain.

It contains the largest population of noradrenergic neurons of the central nervous system; they have a large number of α_2-adrenergic receptors on their membranes. By joining with the agonists by a transmembranal signal, they activate the opening of potassium channels and close calcium channels by voltage, increasing the potassium conductance and decreasing the potassium conductance, resulting in neuronal hyperpolarization and decrease in norepinephrine release[5-7].

The degree of sedation archived by α_2 is dose-dependent. If the sedation is evaluated using the Ramsay scale (level of sedation depending on the patient's response to verbal or tactile stimulation) would be 4, deep sedation with an awakening to the stimulation of high level of consciousness (Table I)[8].

The principal site of analgesic action of α_2-adrenergic agonist is dorsal horn of spinal cord, peripheral and supraspinal structures, different supply routes reach different degrees of antinociceptive effectiveness.

a2-adrenergic receptors are widely distributed in the body; in relation to the location of nociceptive stimuli, they are distributed in nerve, spinal, peripheral and central structures, which are shared with opioids. Stimulation at these sites generates some impairment degree of nociceptive transmission. The extent of this effect will be variable and depend on several factors: type of agonist, the receptor population, the availability of cell intermediates, dose and site of administration.

Pain transmission occurs in the dorsal horn of spinal cord, which depends on different receptors and neurotransmitters

Table I. Ramsay scale.

Patient	Grade
Awake, excited or agitated	1
Awake, quiet, responds	2
Obnubilado, quiet, responds	3
Asleep, respons strongly to verbal or tactile estimulation	4
Asleep, respons lazily to verbal or tactile stimulation	5
Asleep, no responds to stimulation	6

Characteristic of patients, who were administered a sedative drug, assess the level of sedation.

which are combined in this anatomic area and provide an opportunity to interrupt the excitatory transmission and enhance the inhibitory transmission.

Although α_2-adrenergic agonists are diffused also at supraspinal and peripheral level, and it is at the medullary level where they are truly committed, in the excitatory and inhibitory transmission. α_2-adrenergic agonists exert their antinociceptive action at receptors.

α_2-adrenergic presynaptic receptors are linked to primary afferent neurons. When activated, they inhibit sensory transmission, complicating the release from this nerve terminal of the neurotransmitters, these latter are diffused to the second order neurons, the nociceptive information.

α_2-adrenergic postsynaptic receptors cause hyperpolarization by increasing the flow of potassium, delaying the postsynaptic depolarization, and hinder the rostral transmission of pain sensation.

The descending inhibitory pathway (bulbospinal) presents a large number of projections containing and releasing norepinephrine into the nociceptive synapse of this medullary region. The norepinephrine binds to α_2-adrenergic pre- and postsynaptic receptors inducing inhibition of nociceptive transmission.

This norepinephrine's affinity for α_2-adrenergic agonists is overcome by synthetic ligands: Clonidine and dexmedetomidine. It has been found that doses lower than those used in the intravenous route cause a most powerful and lasting analgesia.

The use of α_2-adrenergic agonists with opioids causes what is known as analgesic synergism. The analgesic quality and duration of block is enhanced by combining the agonists and local anesthetics; unlike opioids, this combination don't cause respiratory depression[9-13].

Dexmedetomidine is a lipophilic agent, so it is rapidly absorbed into the bloodstream, causing possibly systemic effects even after subarachnoid administration, it is a drug highly selective for a2-adrenergic receptors in a range of 1,600:230 in relation to the clonidine.

As above mentioned, the binding of these α_2-adrenergic agonists in cortical centers such as *locus coeruleus* creates analgesic and sedative actions which depend on delivered dose, even accomplishing implications on blood pressure and heart rate. It should be borne in mind that the use of dexmedetomidine by spinal route will generate analgesia whose power and duration will depend on the dose of concurrently injected drugs, but also a dose-dependent sedation and hemodynamic effects appear.

A 0.5-1 μg/kg dose of dexmedetomidine by peridural route reduces the latency time of the block, increases the duration of analgesic effect, improves the analgesic quality and causes sedation without causing respiratory depression, although there are studies which used a 2 μg/kg dose[14,15].

With the advent of monitors such as Bispectral Index (BIS), it has been possible to demonstrate that during sedation, using combinations of propofol/benzodiazepines and opioids, when a patient reaches levels of deep sedation (BIS = 60), getting the patient back to superficial levels (BIS> 90) carries a important latency using these drugs. However, despite the patients are in deep sedation levels, when using dexmedetomidine to stimulate them, they reach BIS values greater than 90 and reduced recovery times are observed.

With this background we tried to identify the degree of sedation achieved, as well as hemodynamic changes and analgesia by administrating dexmedetomidine via the epidural route in regional anesthesia.

METHODOLOGY

Descriptive, prospective and longitudinal study was conducted after obtaining the protocol approval by Ethics and Research Committees of the institution, as well as informed consent by patients. We included male and female patients aged 18 to 65 years for surgery on abdomen and lower limbs, the patients were classified as ASA 1 and 2 and underwent locoregional anesthesia. Cardiopathic patient with hypotension and "allergy" to drugs to be used were excluded. The patient was monitored for noninvasive blood pressure (NIBP), continuous electrocardiogram (ECG) on DII, oxygen saturation (SpO_2) in the operating room. A load volume of 10 mL/kg physiological saline was administered to prevent hypotension by sympathetic effect of epidural block.

The anesthetic technique for epidural block (EDB) was performed as following: the patient was placed in lateral decubitus position, by locating spaces from L1-L2 to L3-L4, with asepsis and antisepsis of the region, placing sterile areas, infiltration of local anesthetic at the site of puncture, epidural space was located using the technique of loss of

resistance (Pitkin), local anesthetic (lidocaine plus 2% epinephrine at 3-4 mg/kg doses) was administered along with the dexmedetomidine solution at 1 μg/kg dose via epidural. While the patient was in dorsal decubitus, sedation level was evaluated using the Ramsay's scale during the transoperative period. Hemodynamic changes, the diffusion and degree of analgesia produced by dexmedetomidine during the transoperative period were assessed also, and they were recorded at 5, 10 , 15 and 30 minutes, subsequently every half hour until the end of the anesthetic and surgical events.

When there was any complication, it was treated immediately. When there was bradycardia considered as decrease in baseline heart rate ≥ 20%, 10 mg/kg atropine was administered; in case of hypotension with decrease in blood pressure greater than 20% of the baseline figure, it was treated with prior administration of fluids and 5 mg bolus ephedrine, dose-response relationship. Upon completion of the surgery, the patient was moved to Postanesthesic Care Unit (PACU), recording the Ramsay sedation level when the patient exits.

RESULTS

In total, 40 patients were included, 26 men and 14 women. Using general data described in Table II and the classification of anesthetic risk according to the ASA, 36 and 4 patients were degree II and I, respectively. Moreover, anesthetic and surgical times are described also.

Table II presents the total patients by participant service, and the frequency of surgeries performed in each of the services. The services received by the patients were: 23 patients received orthopedics; 11 patients received general surgery; 2 patients received urology, cardiovascular and thoracic surgery; 1 patient received gynaecology and oncology (Figure 1).

The type of surgery performed by Service of Orthopedics was open reduction and internal fixation, arthroscopy, plasty, and others. Service of General Surgery performed inguinal plasty, umbilical, appendectomy, and debridation. Service of Urology performed radical orchiectomy and persistence resection of peritoneovaginal duct. Service of Cardiovascular performed graft exploration with thrombectomy and bilateral saphenectomy. Service of Oncology performed radical orchiectomy and Service of Gynaecology performed washing and surgical wound closure.

The puncture level of RMB was L1-L2 (22.5%), L2-L3 (75%) and L3-L4 by 2.5%. Lidocaine with epinephrine at 3 to 4 mg/kg doses plus 1 μg/kg dexmedetomidine was administrated epidurally. Lidocaine with epinephrine at 3 mg/kg dose was administrated to 25 patients, water for injection was added to 4 mg/kg doses administrated to the remaining patients until reaching the total volume of 15 mL. Used maximum and minimum doses of the drugs were 320 and 150 mg for lidocaine plus epinephrine, 110 and 50 mg for dexmedetomidine. It was necessary to administrate a extra dose of lidocaine plus epinephrine within 32 minutes in 11 patients in group of 3 mg/kg dose; additionally it was necessary to administrate a extra dose of lidocaine plus epinephrine within 70 minutes in 4 patients in group of calculated dose of 4 mg/kg.

The diffusion level of PDB achieved in the patients was T4 (6 patients), T5 (7 patients), T6 (15 patients), T7 (2 patients), T8 (4 patients), T9 and T10 (2 patients) and T11 (1 patients). In one case it was not possible to measure the diffusion, since the patient had Ramsay sedation level 5, arousing to gentle mild tactile and verbal stimulus, however the patient did not cooperate. When a patient indicated inconvenience due the pulling, fentanyl at 2 μg/kg dose

Percentage of surgical departments, in the study.

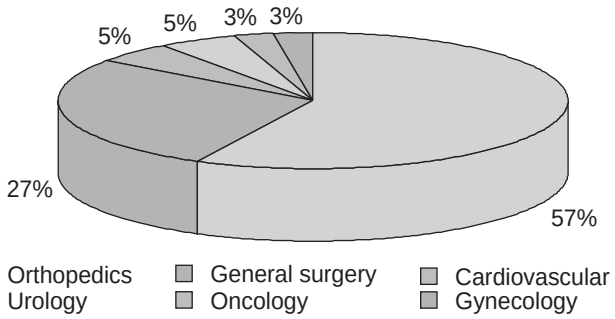

Figure 1. Services involved with the highest percentage of patients are Orthopedics and General surgery.

Table II. Anthropometric data.

	age (years)	Weight (kg)	Height (m)	Sex (%)	ASA (%)	T. An (min)	TQx (min)
Average	35.6	72	1.64			115	83
Maximus	65	112	1.89	M 65	I 10	225	195
Minimal	18	50	1.48	F 35	II 90	35	25

Description of average ranks of general characteristics of population.

was administered, the volume administered in this patient was a total of 8 mL. Another patient was given 1 mg midazolam plus 0.5 mg/kg ketamine for non-cooperation, the patient did not indicated pain only showed restlessness.

The hemodynamic data obtained after the block on heart rate (HR) showed a gradual decline from the first 5 minutes. The lowest HR at 60 minutes was of 17% as compared to baseline HR, keeping on average the HRs between 10% and 14% below the baseline value. Only 3 patients required the atropine administration at a 10 μg/kg dose, because the decline in HR was up to 25% (Figure 2).

Mean blood pressure also showed decrease in the figures, the biggest fall was observed from 60 to 150 minutes with variations from 18 to 22% in both the SBP and the DBP; MBP decreased to 20% in this time. Two patients required the administration of 5 mg ephedrine due to decreases higher than 20% (Figure 3).

The sedation of patients was managed with a single dose of epidural dexmedetomidine, no subsequent dose was administered. The sedation was observed from 5 minutes and was maintained throughout the surgery, even before the complete induction of the PDB. During the anesthetic procedure, the patients were stimulated in a gentle tactile and verbal manner, obtaining adequate response and showing a sedation level of 2 on Ramsay sedation scale at the time. In patients who achieved a sedation level of 2 on Ramsay sedation scale, even with incomplete induction of motor block, it was possible to initiate the surgical procedure. On the other hand, complete recovery of motor block was observed after surgery and there was still sedation (Ramsay 4) without pain or discomfort.

Table III shows the degree of sedation observed in each patients after the epidural administration of dexmedetomidine. In total, 17% of them had sedation level of 3 on Ramsay sedation scale within 5 minutes; 90% of them had sedation level of 3-4 on Ramsay sedation scale from 15 to 90 min; 4 patients had sedation level of 5 on Ramsay sedation scale from 30 to 60 minutes during 30 minutes. After the 60 minutes, the sample began to decrease due the end of surgery, but still retained the

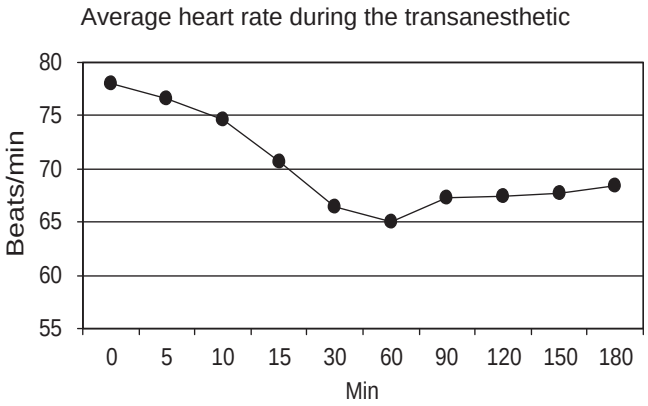

Figure 2. One of the adverse effects of dexmedetomidine is bradycardia, which as noted, no show at dose of 1 μg/kg, the biggest fall is in 60 minutes.

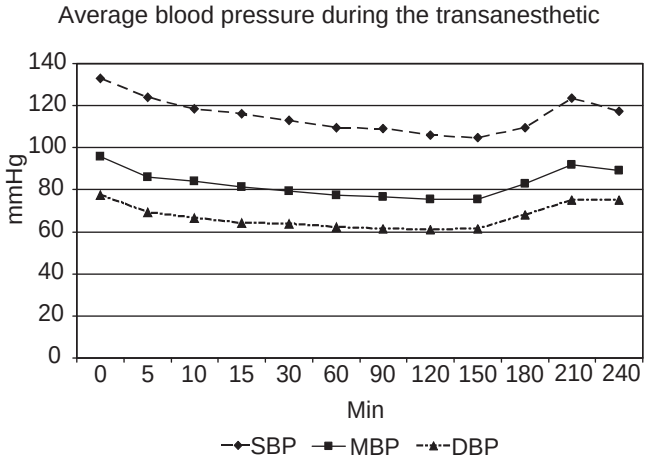

Figure 3. Hemodynamic behavior of patients is stable, the percentage of hypotension is no more than 20% with respect to basal line.

Table III. Frequency of the degree of sedation, measured by the scale of Ramsay during surgery.

Grade	5´	10´	15´	30´	60´	90´	120´	150´	180´	210´	240´
1 (*f*)	1	1		2		1					
2 (*f*)	32	18	4	3	2	6	11	3	3	0	
3 (*f*)	7	16	21	6	8	8	5	1			
4 (*f*)		4	15	25	26	17	6	4	2	2	2
5 (*f*)				4	4						

Frequency of the degree of sedation measured by the scale of Ramsay, was between 2 and 4, wich is the optimum (referred by the autor of the scale) although 10% was 5.

same level of sedation. Adequate sedation was maintained between 10 and 120 minutes with a single dose.

After PDB, the grade 3 motor block was achieved from 15 to 90 minutes in more than 90% of the population. After 60 minutes the sample decreased due differences in surgical and anesthetic times, but the grade 2-3 motor block remained, as shown in Table IV.

The mean duration of the dose was 131.25 minutes (maximum of 300 minutes and minimum of 60 minutes, with a range of 240 min), considering as sensory block onset time from the moment in that the dose was administered, and as sensory block conclusion time from the moment in that discomfort or regression of two metameres was reported.

By calculating χ^2_{cal} with 12 degrees of freedom = 52.80, χ^2_{tab}, with a significance of 0.05, the result is 21.05, therefore we can conclude that Ramsay sedation level of 3-4 is produced by peridural administration of dexmedetomidine, so it is statistically significant, p 0.05.

DISCUSSION

The use of α_2-adrenergic agonists has been basically with clonidine, but the introduction of dexmedetomidine, which is highly selective, has attracted interest for its use in anesthetic procedures, mainly by intravenous route, due to its qualities (analgesic, sedative and amnesiac), decreasing consumption of anesthetics. However, it has side effects mainly hypotension and bradycardia, possibly also hypertension, antisialogogue effect and fever, which were not observed in this study group[3,4,12].

Antonio Maura et al. in their study of "Clonidine and dexmedetomidine via epidural for postoperative analgesia and sedation in cholecystectomy", included 40 patients with features similar to those in this study. PDB was installed in the patients by administering 2 μg/kg dexmedetomidine, 150 μg clonidine plus 0.75% ropivacaine to 20 patients, followed by balanced general anesthesia. Degree of sedation was monitored in the postoperative period using Filos' scale (1. Conscious and nervous; 2. Conscious and quiet; 3. Sleepy with easy arousal; and 4. Sleepy with difficult arousal) and analgesia was monitored using the visual analog scale. Statistically significant differences were found between groups in relation to sedation and analgesia, this differences were favourable for dexmedetomidine. In the group of patients studied here, the epidural dexmedetomidine administration is lower (1 μg/kg), by which we can infer that the drug effectively inhibits transmission of nociceptive signals through the spinal cord when it joins to pre-and postsynaptic receptors, causing sedation, analgesia and a adequate quality of anesthesia, as mentioned with lower doses of local anesthetic. Sensory block is installed quickly, in which the surgical area can be manipulated, no matter which the motor block is not fully installed[14,15].

The probability of respiratory depression when using anxiolytic drugs during locoregional anesthesia in this form of administration is decreased significantly, as the level of sedation achieved is adequate, thus easily returning the patient to Ramsay sedation levels 2 with verbal stimuli. However, Ramsay sedation levels 5 can be achieved, which leads to a less cooperation, which was 10% in this sample. Sedation obtained by using epidural dexmedetomidine is as described by Dr. Scafatti "*active sedation*". The likelihood of causing hypotension and bradycardia during this procedure is minimized by using a water load, as well as reducing the amount of local anesthetic to reduce the synergism of drugs, in case there is (incidence of 5% was observed for these 2 situations in this group), they are easily reversible by administrating atropine and ephedrine, as demonstrated in this group, as reported by Dr. Higgins[11,12].

CONCLUSIONS

The use of dexmedetomidine by peridural route at 1 mg/kg dose plus local anesthetics is an alternative to achieve an anesthetic quality that enables us to keep the patient in a state of *active sedation*, which reduces the likelihood of respiratory depression, which can arise when adjuvants drugs are administered intravenously. It also reduces the doses of local anesthetics, as it potentiates the effects of both drugs, with consequent reduction of their adverse effects.

Table IV. Frequency of the degree of motor block measured by the Bromage scale, after administration of peridural dexmedetomidine.

Bromage	5'	10'	15'	30'	60'	90'	120'	150'
0	20	0	0	0	0	0	0	0
1	15	16	2	0	0	0	0	0
2	4	17	14	3	2	4	10	2
3	1	7	24	37	38	27	11	5

The degree of motor block describes the effect of lidocaine, starting your installation to 10 minutes, lasted approximately 2 hours.

REFERENCES

1. Miller RD. Anesthesia. Fourth edition. San Francisco California. Harcourt Brace, 1998:268-269.
2. Goodman, Gilman. Pharmacological bases in therapeutics. Ninth edition. Mexico, D.F. McGraw-Hill Inter-American, 1996:349.
3. Ribeiro RN, Nascimento JP. The use of dexmedetomidine in anesthesiology. Rev Bras Anestesiol 2003;53:1,97-113.
4. Kamibayashi T, Maze M. Clinical uses of α_2-adrenergic agonists. Anesthesiology 2000;93:1345-1349.
5. Mato M, Pérez A, Otero J, Torres LM. Dexmedetomidine, a promising drug. Rev Esp Anestesiol Reanim 2002;49:407-420.
6. Linde H e Mo. The clinical use of dexmedetomidine. Rev Bras Anestesiol 2004:1-4.
7. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg 2000;90:699-705.
8. Ramsay MA, Savage TM, Simpson BR, Goodwin R. Controlled sedation with alphaxolone-alphadolone. Br Med J 1974;2:656-659.
9. Thomas JE. New tendencies in sedation. Medens Review 2003: 16-18.
10. Scafati A. Active sedation. Medens Review 2003:4-8.
11. Higgins L. Alpha agonist 2 in spinal blockade (block). Medens Review 2003:9-11.
12. Scafati A. Analgesia and alpha agonists 2. Medens Review 2004: 4-7.
13. Cortinez L, Yung-Wei H, et al. Dexmedetomidine pharmacodynamics: Part II. Anesthesiology 2004:1066-1075.
14. Mauro VA, Brandão ST, et al. Clonidine and dexmedetomidine through epidural route for post-operative analgesia and sedation in a colecistectomy. Rev Bras Anestesiol 2004;4:1-10.
15. Brandão ST, Mauro VA, Aguiar BA, Tonante LM. Intra-operative analgesic effect of cetamine, clonodine and dexmedetomidine, administered through epidural route in surgery of the upper abdomen. Rev Bras Anestesiol 2005;55:5,525-231.