Egyptian Journal of Anaesthesia (2014) **30**, 305–310

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

The effect of ondansetron in preventing the hypotensive bradycardic events during shoulder arthroscopy done under interscalene block in the sitting position

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Received 5 October 2013; revised 2 February 2014; accepted 4 February 2014
Available online 28 February 2014

KEYWORDS

Ondansetron;
Hypotensive bradycardic events;
Shoulder arthroscopy;
Sitting position;
Interscalene block

Abstract *Purpose:* This study was conducted to test whether blocking the serotonin receptors by intravenous [IV] ondansetron; can help in reducing the hypotensive bradycardic events [HB events] associated with shoulder arthroscopy done in the sitting position under interscalene plexus block [ISB].

Methods: One hundred and fifty patients, scheduled for shoulder arthroscopy in the sitting position under ISB, were randomly assigned to one of three groups receiving either: 4 mg ondansetron, or 8 mg ondansetron or saline.

Results: IV injection of ondansetron 4 mg or 8 mg significantly reduced the incidence of HB events from 20.4% in the saline group to 6.1% after injection of 4 mg ondansetron and 6% after injection of 8 mg ondansetron; *p* value [0.030].

Conclusion: IV ondansetron either 4 mg or 8 mg reduces the HB events during shoulder arthroscopy in the sitting position under ISB.

1. Introduction

Arthroscopic shoulder surgery is now preferred to be done in the sitting position [1,2], under interscalene brachial plexus blockade (ISB) [3,4]. ISB is an effective anesthetic technique for shoulder surgery [3]. ISB reduces the hospital stay [5], and the need for postoperative analgesics [2,6]. Patients undergoing ISB also experience high levels of satisfaction with their anesthesia [7].

Although ISB has been shown to be successful when done by skillful anesthesiologists, but resistance to its use still

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

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presents because of hemodynamic changes in the form of sudden bradycardia and/or hypotension (HB) events, frequently associated with nausea and/or lightheadedness that have been seen in 13–29% of patients who received ISB for shoulder arthroscopy in the sitting position [8,9].

These HB events may be a form of vasovagal syncope mediated by the Bezold–Jarisch reflex (BJR), which happens when venous pooling and increased sympathetic tone cause a low-volume, hyper contractile ventricle [9–11]. This leads to sudden activation of the parasympathetic nervous system and sympathetic withdrawal, causing bradycardia and hypotension.

Animal studies reported that serotonin (5-HT), may be an important contributing factor to the occurrence of BJR in the settings of decreased blood volume [12,13], which can be blocked by antagonizing the serotonin at the level of the receptors [14]. Also Owezuk et al. [15] reported that intravenous ondansetron attenuated the spinal induced hypotension that might be caused by BJR.

We hypothesized that blocking the serotonin receptors by ondansetron [a selective 5-hydroxy tryptamine 3 (5-HT3) receptor antagonist] can help in reducing the HB events associated with shoulder arthroscopy done in the sitting position under ISB.

2. Materials and methods

After obtaining approval from our ethical committee written informed consent was obtained from 150 patients with ASA physical status I or II; who were scheduled for shoulder arthroscopy in the sitting position under ISB, at Saad Specialist Hospital, Alkhobar, Saudi Arabia, between June 2011 and December 2012.

One hundred and fifty patients were assigned to one of three equal groups receiving either the following:

- 4 mg ondansetron (group I) diluted in 10 ml normal saline.
- 8 mg ondansetron (group II) diluted in 10 ml normal saline
- 10 ml normal saline group (group III).

All the tested drugs were injected over 1 min, 5 min before starting the ISB.

Randomization was performed using random computer allocation with numbered envelop. The syringes were prepared by a technician anesthetist who was not involved in the study.

The power analysis was done using the reported incidence of HB events of 24% [16]; which revealed that 150 patients were needed to detect 50% decrease in these events with 95% confidence limit.

Patients were excluded if they refused the ISB, had coagulation disorders, sensitivity to local anesthetic, severe chronic pulmonary disease, coronary heart disease, arrhythmias, neuropathy or neurologic deficiency at the site of the procedure, infection at the site of injection, uncooperative patients, patients with history of chronic pain and patients receiving beta blockers or calcium channel blockers.

Immediately after arrival to the operating room; intravenous cannula was inserted and non-invasive monitoring of blood pressure, oxygen saturation, and electrocardiogram were applied to all patients and their baseline vital signs were measured. All patients received midazolam 0.03 mg/kg IV, and fentanyl 1 μg/kg IV, 10 min before the block. All patients received oxygen through nasal cannula at a rate of 2 L/min.

After confirming the proper site of the operation; all patients were put semisetting with their head turned to the opposite side of the block.

ISB was done under the guidance of both nerve stimulator and ultrasound using 30 ml of 0.5% bupivacaine.

After proper sterilization of the skin; the linear ultrasound probe was draped with disinfected wrap and gel was applied; and we screened for the round to oval-shaped honeycomb appearance of hypoechoic nerve roots in short-axis view located between anterior and middle scalene muscles using a 5–12 MHz linear probe of ultrasound (SonoSite M-TurboTM, SonoSite, Bothell, USA). Two milliliters of lidocaine 1% were injected subcutaneously to anesthetize the skin using 25-gauge needle. A 22 G 50 mm length insulated needle (Stimuplex®, B. Braun Melsungen, Melsungen, Germany) connected to a nerve stimulator (Stimulplex DIG®, B. Braun, Melsungen, Germany) was used via the in-plane method. The local anesthesia (LA) for each group was slowly administered after twitch confirmation from the deltoid, pectoralis major, triceps, or biceps through 2 Hz after reducing the initial current from 1.2 mA to less than 0.5 mA of electrical stimulation, and after negative aspiration of blood. Diffusion of LA was observed with ultrasound, and needle position was adjusted to surround all nerve roots with LA.

All ISB were done by one anesthesiologist, and all surgeries were performed by the same surgeon.

After the ISB was done, noninvasive blood pressure (BP) was measured every 5 min with more frequent measurement if needed, and continuous ECG monitoring. Then the patients were placed in the sitting or ''beach chair'' position, which was achieved by elevating the back of the operating room table to 60–80° and flexing both the knees and hips to 90° with the patients' feet resting properly on a footboard.

Sensory blockade was evaluated every 5 min by pinprick test in the area of distribution of the circumflex nerve, musculocutaneous nerve, and radial cutaneous nerve of the arm. Sensory blockade was defined when there was no sensation to pin prick test. However, motor block was tested by asking the patient to raise his arm (circumflex nerve), to abduct/adduct the thumb (radial/ulnar nerves) and to flex the forearm on the arm (musculocutaneous nerve).

The block onset time was defined as the time elapsed between the end of injection and the achievement of complete sensory and motor block (surgical anesthesia).

Intraoperative sedation with midazolam boluses of 0.02 mg/kg if needed, fentanyl 1 μg/kg boluses were given only if the patient complaint of pain. The amount of midazolam and fentanyl and the degree of sedation were recorded (sedation score: 1 = awake, 2 = awake but sedated, 3 = asleep but responsive to verbal stimuli, and 4 = asleep but responsive to tactile stimuli). Total intravenous fluid was limited to 10–12 ml/kg.

HR and BP were recorded by anesthesiologist blinded to the study drugs. A BH event was defined by Liguori et al. [10], if HR decreased more than 30 bpm in less than 5 min or any decrease less than 50 bpm, and/or a systolic BP decrease more than 30 mmHg in less than 5 min or any decrease to less than 90 mmHg. This event was managed by intravenous injection of atropine (0.5 mg boluses) or ephedrine (5 mg boluses).

Lightheadedness, nausea, and sweating were recorded but were not essential in defining a HB event.

After the recovery, a doctor blinded to the study groups tested and recorded the pain using the verbal numerical rating scale (VNRS: 0 = no pain, 10 = most severe pain imaginable); starting immediately on arrival to the recovery room as 0 h and 1, 3, 6, 12 h later. When the VNRS was more than 3, IV pethidine 0.5 mg/kg was injected and recorded. Duration of analgesia was defined by the time interval between achievement of surgical anesthesia and the 1st administration of pethidine (VNRS >3).

Any complications as neurological disabilities, nausea, vomiting or respiratory difficulties were also recorded.

Data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using one way analysis of variance (ANOVA) test. Pairwise post hoc comparisons were done using Student's t test with Bonferroni adjustment for multiple comparisons. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. p values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

One hundred and fifty patients were randomized equally to three groups. Two patients were excluded from the study due to block failure one of them was randomized to group I and the second one was randomized to group III, yielding 49 patients in group I, 50 patients in group II and 49 patients in group III. There were no differences between the groups regarding age, sex, weight, height, ASA physical status, side of surgery, and baseline HR and BP; p value >0.05. (Table 1).

There were no symptoms suggestive of spinal, epidural or stellate ganglion blockade or intravascular injection in three groups.

Patients in the three groups were comparable with regard to their baseline blood pressure, baseline heart rate, sedation score, NPO and IV fluid; p value >0.05, (Table 2).

HB events were recorded in 3 patients in group I (6.1%), 3 patients in group II (6%) and 10 patients in group III (20.4%) which was significantly higher than in groups I and II ; p value (0.030) Table 2. The onset of these HB events was comparable in the three groups, Table 2. Ten patients in group III received ephedrine to treat hypotension which was significantly higher comparing to the other two groups; 3 patients in group I and 3 patients in group II; p value (0.030), Table 2. One patient in group I, two patients in group II and five patients in group III needed atropine to treat bradycardia, p value (0.175), Table 2.

There was no significant difference in the use of intraoperative midazolam or fentanyl; p value >0.05, Table 2.

There was no significant difference in the block onset time in the three groups; (20.9 ± 5.6 min), (22.1 ± 2.5 min) and (22.3 ± 3.5 min) in groups I, II and III respectively; p value (0.186), Table 3.

The duration of analgesia was significantly longer in group III (8.9 ± 4.9 h) in comparison with groups I and II (6.1 ± 7.4 h) and (6.9 ± 3.3 h); p value (0.035), Table 3.

4. Discussion

The main purpose of this study was to test the hypothesis that intravenous ondansetron would reduce the incidence of HB events in arthroscopic shoulder surgery in the sitting position after ISB. Activation of the BJR is considered one of the proposed mechanisms for the occurrence of HB events [9,17,18]. The BJR is an inhibitory reflex that originates in the cardiac sensory receptors with vagal afferents that are affected by chemical and mechanical stimuli [19].

Although the mechanism of BJR during shoulder arthroscopy has been explained by D'Alessio et al. [9] who pointed that it may be caused by venous blood pooling (induced by the sitting position) and an increase in cardiac contractile state (induced by the β-adrenergic effects of epinephrine) which causes reflex arterial vasodilation (mediated by the activation of the parasympathetic nervous system) and a subsequent vagally-mediated bradycardia .Increased epinephrine may be caused by decreased venous return due to sitting position and stimulation of the carotid baroreceptors (endogenous epinephrine).

Hypovolemia not only causes stimulation of cardiac mechanoreceptors in the left ventricle that triggers the BJR and causes reflex bradycardia, vasodilatation and hypotension [19–22], but also results in the activation of thrombocytes to release serotonin which triggers chemoreceptors in the wall of the heart [12,21,23]. Furthermore, stimulation of 5-HT3 receptors, that are G protein coupled, ligand-gated, fast-ion channels, increases the activity of the vagal nerve [21].

Yamano et al. [24,25] reported that BJR induced by serotonin participates in systemic hypotension and bradycardia in anesthetized rats . This means that BJR can also be directly triggered by the activation of the serotonin 5-HT3 receptors.

Based on these studies we assumed that preventing the effect of serotonin by blocking 5-HT3 receptors by intravenous ondansetron can help in reducing the incidence of the HB events associated with shoulder arthroscopy done in the sitting

Table 1 Demographic data.

	Group I (n = 49)	Group II (n = 50)	Group III (n = 49)	P value
Age (yr)	46.7 ± 3.1	48.1 ± 4.2	47.0 ± 2.1	0.082
Weight (kg)	69.5 ± 2.5	68.7 ± 2.5	69.10 ± 1.1	0.181
Height (cm)	162.2 ± 7.3	163.5 ± 9.1	164.1 ± 6.3	0.457
Gender (m/f)	28/21	29/21	28/21	0.995
ASA (I/II)	40/9	42/8	41/8	0.944
Side of surgery (R/L)	29/20	31/19	28/21	0.885

Data are expressed as mean ± SD or numbers.

Table 2 Intraoperative data.

	Group I (n = 49)	Group II (n = 50)	Group III (n = 49)	P value
Baseline HR (bpm)	80.0 ± 15	77.4 ± 16	80.4 ± 11	0.521
Baseline systolic BP (mmHg)	124.2 ± 10	127.1 ± 11	125.0 ± 12	0.403
Sedation score[a]	1.94 ± 0.07	1.93 ± 0.06	1.92 ± 0.08	0.375
NPO (min)	696.6 ± 18	700.3 ± 15	693.4 ± 11	0.075
IV fluid (Ml)	489.0 ± 45	500.4 ± 32	487.7 ± 65	0.369
HB events (n, %)	3 (6.1%)	3 (6%)	10 (20.4%)	0.030*
Onset of HB events from ISB (min)	43.6 ± 5.5	44.1 ± 2.7	44.5 ± 2.7	0.514
Onset of HB events from sitting position (min)	13.3 ± 3.6	14.0 ± 1.1	13.7 ± 3.1	0.463
Intraoperative drugs				
Ephedrine	3	3	10	0.030*
Atropine	1	2	5	0.175
Midazolam	2	3	2	0.874
Fentanyl	0	1	1	0.609

Values are expressed as mean ± SD, number or %.
HR = heart rate, BP = blood pressure, HB events = hypotensive and/or bradycardiac events, ISB = interscalene block.
[a] Scale of 1–4 (1 = awake, 2 = awake but sedated, 3 = asleep but responsive to verbal stimuli, 4 = asleep but responsive to tactile stimuli).
* p value < 0.05.

Table 3 Block onset time and analgesia duration.

	Group I (n = 49)	Group II (n = 50)	Group III (n = 49)	P value
Block onset time (min)	20.9 ± 5.6	22.1 ± 2.5	22.3 ± 3.5	0.186
Duration of analgesia (h)	6.1 ± 7.4	6.9 ± 3.3	8.9 ± 4.9	0.035*

Data are represented as mean ± SD.
* p value < 0.05.

position under ISB. To the best of our knowledge, this is the first study to evaluate the effect of serotonin receptor antagonists on reducing the incidence of HB events in arthroscopic shoulder surgery in the sitting position after ISB.

Our results demonstrated that IV injection of ondansetron 4 mg or 8 mg significantly reduced the incidence of HB events in our patients; from 20.4% in the saline group (group III), to 6.1% after injection of 4 mg ondansetron (group I), and 6% after injection of 8 mg ondansetron (group II).

This 20.4% incidence of HB events in the saline group is consistent with the previous reports of such events. Roch and Sharrock reported 24% incidence of HB events, D'Alessio et al. [9] reported a 21% incidence and Liguori et al. [10] reported the incidence of 27.7% incidence in the placebo group.

The reduction in HB events in our study after IV ondansetron is in agreement with that of White et al. [26] who observed that IV administration of granisetron 50 μg/kg in rabbits was efficacious in reducing bradycardia and hypotension associated with BJR.

Also; Tsikouris et al. [27] found that granisetron injection reduced the heart rate fluctuation and hypotension during head-up tilt table tests that are likely related to BJR.

And this is consistent with Matrinek [12] who concluded that injection of 4 mg ondansetron i.v. with atropine 0.6 mg could revert asystole during spinal anesthesia and also with Owezuk et al. [15] who found that 8 mg ondansetron reduced the incidence of bradycardia and hypotension after spinal anesthesia.

ISB can cause hypotension by its side-effects including a spinal or epidural blockade and/or a stellate ganglionic block. Sympathetic blockade due to ISB may attenuate the compensatory response caused by the sitting position [28]. We could not observe any signs of extensive spread of local anesthetic to the epidural or subarachnoid space, no contralateral arm weakness or apnea in any of our patients.

Although intravenous uptake of local anesthesia can be considered as a cause of hemodynamic instability, but the time of onset of hypotensive bradycardic events from the block was (43.6 ± 5.5 min, 44.1 ± 2.7 min and 44.5 ± 2.7 min) in groups I, II and III respectively, which is longer than what would be expected for the peak uptake for the bupivacaine injected in the block, which is approximately 30 min [29,30]. Furthermore, the central nervous system symptoms such as lightheadedness, nausea and vomiting resolved completely after treatment with ephedrine or atropine.

Previous studies reported interval between positioning and hemodynamic changes ranging between 12 and 24 min but may be delayed to 1 h [31,32]. Our patients had similar sequence of events to those undergoing tilt-table testing, and the onset of symptoms was (13.3 ± 3.6 min), (14.0 ± 1.1 min), (13.7 ± 3.1 min), in groups I, II and III, respectively.

Although onset of analgesia was similar in all groups, the duration of analgesia was shorter in groups I and II in comparison with group III. This can be explained by antagonizing the effect of serotonin in controlling pain. Although potential mechanisms of this observation were not clear, but animal studies have clarified the antinociceptive mechanisms of the descending serotoninergic system at the level of the spinal cord [33,34]. It hyperpolarize the membrane of substantia gelatinosa neurons, inhibits the excitatory transmitter glutamate release of Aδ and C afferent fibers presynaptically and increases the

inhibitory transmitters release including -aminobutyric acid and glycine from the interneurons [34].

The shortened duration of analgesia observed in our study is consistent with Fassoulaki et al. [35] who reported that IV ondansetron leads to a faster regression of the sensory block after spinal anesthesia with lidocaine. Also, continuous IV administration of ondansetron decreased the analgesic potency of tramadol infusion for postoperative pain [36].

The combination of sitting position, ISB, and surgical procedure may result in HB events, usually, of minor significance if anticipated, but in extreme cases, it can lead to profound hypotension and bradycardia. Therefore, we suggest the use of 5-HT3 antagonists as ondansetron to reduce the incidence of HB events.

We conclude that intravenous ondansetron either 4 mg or 8 mg can reduce the hypotensive bradycardic events during shoulder arthroscopy in the sitting position under ISB.

Limitations to this study include the long fasting hours and the limited amount of fluids given during surgery which could have increased the incidence of hemodynamic instability in our patients. Probably, perioperative administration of a larger amount of IV fluids might have reduced HB events in some patients of all groups. But this approach may lead to discomfort due to urinary bladder distention.

Further studies are needed to be done on smaller doses of ondansetron as 0.05 mg/kg which was used effectively in reducing nausea and vomiting [37]; also further studies are needed on other 5-HT3 antagonists.

Conflict of interest

None.

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