Addition of adenosine to hyperbaric bupivacaine in spinal anaesthesia does not prolong postoperative analgesia in vaginal hysterectomy

Ghai A, MD
Hooda S, DA, MD
Saxena S, MD
Garg N, MD
Department of Anaesthesiology, PGIMS, Rohtak, Haryana, India
Wadhera R, MS
Department of Otorhinolaryngology, PGIMS, Rohtak, Haryana, India
Correspondence to: Dr Anju Ghai, e-mail: dr.wadhera@yahoo.com
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Abstract

Background: Systemic administration of adenosine produces anti-nociception. Although literature supports intrathecal adenosine for neuropathic pain, its efficacy in postoperative pain remains unproven. There has been no study on the efficacy of adenosine on postoperative pain when administered with hyperbaric bupivacaine. The aim of our present study was to evaluate the efficacy of two different doses of intrathecal adenosine as an adjunct to 0.5% hyperbaric bupivacaine in patients undergoing vaginal hysterectomy under spinal anaesthesia.

Method: Seventy-five women, aged 40-60 years and scheduled for vaginal hysterectomy under spinal anaesthesia, were included. Patients were allocated to three groups of 25 patients each to receive 500 µg adenosine (group I), 1000 µg adenosine (group II) and normal saline (group III) with 2.6 ml of 0.5% hyperbaric bupivacaine. Postoperative analgesia was provided with patient-controlled fentanyl. Time of administration of rescue analgesia and total dose of fentanyl were recorded. The times to full recovery of sensory and motor block were noted.

Results: There were no differences in time to rescue analgesia and postoperative fentanyl consumption over 24 hours among the groups. There was no significant difference in onset of sensory and motor block or regression of sensory block, although statistically significant difference was noted in the time taken for regression of motor block.

Conclusion: Intrathecal adenosine does not affect the postoperative analgesic requirement when administered with hyperbaric bupivacaine.

Introduction

Acute pain is an expected outcome after surgery. Results of one survey indicate that approximately 80% of patients who undergo surgery experience severe acute pain during the postoperative period.[1] To improve pain relief and reduce the incidence of side-effects, a multimodal approach is used which involves the use of different classes of analgesics, administered at different sites, and incorporating adjunct analgesics.[2] Various drugs have been used as adjuncts to local anaesthetics in spinal anaesthesia. These include opioids, clonidine, neostigmine, magnesium sulphate, ketorolac and ketamine. The use of intrathecal opioids is associated with dose-related adverse effects such as respiratory depression, nausea, vomiting, urinary retention, itching and sedation.[1] Intrathecal α_2-adrenergic agonists may

cause sedation, hypotension and bradycardia. Intrathecal neostigmine may elicit nausea and hallucinations.[3] Hence there is a need to evaluate better adjuncts to spinal anaesthesia with lesser side-effects.

Adenosine is an endogenous purine nucleoside with several biological effects, both on the peripheral and central nervous system. It is a metabolic intermediate in the body, which is present in all types of body fluids and is involved in nearly every aspect of cell function, including neurotransmission and neuromodulation. This is achieved by acting on adenosine in the spinal cord and periphery through specific cell surface-associated adenosine receptors, which have been identified at spinal level and divided into two main classes, A_1 and A_2.[4] Adenosine has recently been used systemically and intrathecally for the treatment of various

pain states. Perioperative infusion of low-dose adenosine in recent studies has been found to reduce the requirements of inhalation anaesthetics, as well as the total amount of analgesics used.[5-7] The maximum approved bolus dose is 2 mg, as per the Food and Drug Administration regulations.[8]

Studies have shown that intrathecal adenosine reduces pain from stimulation in areas of allodynia, whereas the same dose of adenosine intravenously is ineffective.[9] These studies suggest that intrathecal adenosine may play a role in pain management. However, only three studies of its role in acute pain have been published so far.[10-12] The authors concluded that intrathecal adenosine 500 μg in one study[10] and 1 000 μg in another study[11] did not influence the requirements of anaesthetics and postoperative analgesics. The authors in the third study concluded that adding 500 μg of adenosine to 10 μg sufentanil did not prolong pain relief during labour.[12] No serious side-effects have been reported in humans. To the best of our knowledge, there has been no study on the effect of adenosine on postoperative analgesic consumption when administered as an adjunct to hyperbaric bupivacaine in spinal anaesthesia.

Hence, this study was planned to evaluate the efficacy of intrathecal adenosine following vaginal hysterectomy. The second objective of the study was to evaluate its effects on the onset and regression of sensory and motor blockade and duration of spinal anaesthesia.

Method

Seventy-five American Society of Anesthesiologists (ASA) grade I and II women in the age group 40-60 years, scheduled for vaginal hysterectomy under spinal anaesthesia, were randomised in a double-blind prospective manner. Patients were excluded if they had a history of gout, chronic analgesic therapy, hepatic, renal or endocrine abnormalities, pathological conditions of the lower back, or ingestion of methylxanthine-containing food or beverages within 12 hours of surgery. The patients were visited on the day before surgery and instructed about the use of a linear visual analogue scale (VAS; 0-10 cm), where 0 represented no pain and 10 the worst imaginable pain. They also received training in patient-controlled analgesia (PCA). Premedication was given in the form of alprazolam 0.25 mg the previous night and on the morning of surgery.

On arrival at the operating room, an intravenous line was established, with Ringer's lactate. Routine anaesthetic monitoring included continuous lead II electrocardiogram, pulse oximetry and heart rate and noninvasive blood pressure measurement every five minutes. Patients were randomly allocated, using a computer-generated table of random numbers, to one of three groups to receive with 2.6 ml of 0.5 % hyperbaric bupivacaine either 500 μg adenosine (group I), 1 000 μg adenosine (group II) or normal saline (group III). The total volume of the spinal injectate was 3.2 ml.

Each patient had an envelope bearing the group allocation according to randomisation, which was handled by the assisting nurse. The syringe was presented to the investigator without showing the label. An insulin syringe was used to measure adenosine, and saline was added in group I and III to maintain blinding. We used preservative-free adenosine solution (Carnosin®, Samarth Life Sciences, Mumbai, India). Spinal anaesthesia was administered with 25 G Quincke spinal needle using a midline approach at the L3-L4 or L4-L5 intervertebral space in the sitting or lateral position. Patients were made to lie in the supine position for 10 minutes, after which the lithotomy position was assumed, and continuous monitoring for heart rate, blood pressure, electrocardiography and oxygen saturation was conducted intraoperatively. Haemodynamic parameters were recorded in all patients throughout the surgery. The time of the intrathecal administration of the study drug was taken as time zero. The level of sensory anaesthesia was recorded at five-minute intervals after completion of intrathecal injection until two consecutive readings were the same, then every 30 minutes for one hour, every 20 minutes in the second hour and, thereafter, every 15 minutes until the sensory level regressed by two segments.

The degree of the motor blockade was assessed during surgery and graded using the Bromage scale (0: full flexion of feet and knees, 1: just able to move knees, 2: able to move feet only, and 3: unable to move feet or knees) at the same intervals.[13] Patients requiring general anaesthesia, either for incomplete block or for prolonged surgery, were excluded from statistical analysis. During surgery, episodes of desaturation, hypotension (blood pressure less than 15% of baseline) and dysrhythmias were noted. Intravenous mephentermine was used to treat hypotension. The duration of surgery was noted and the total dose of mephentermine required was recorded.

On arrival at the postanaesthetic care unit, rescue analgesia was administered with a bolus dose of fentanyl 2 μg/kg at VAS score greater than three, and the time to the first complaint of pain was noted. All patients were connected to a PCA fentanyl device (10 μg/ml) and a dose of 10 μg was delivered on the patient's demand, with a lockout interval of 10 minutes. In case of inadequate analgesia, the dose was increased to 20 μg at any time. The patients were evaluated for pain scores, heart rate, noninvasive blood pressure, sedation and side-effects hourly for the first two hours, two hourly for the next 12 hours and then three hourly up to 24 hours.

Sedation was assessed on a four-point scale (wide awake: 0, sleeping comfortably but responding to verbal commands: 1, deep sleep but arousable: 2, deep sleep and unarousable: 3).[14] The maximum pain scores at different time intervals (0-6, 6-12, 12-18 and 18-24 hours) for each patient were considered for statistical analysis. Side-effects in the form of nausea, vomiting, respiratory

depression (oxygen saturation less than 90% or respiratory rate less than eight breaths per minute) and lumbar pain were noted. In case of nausea and vomiting, intravenous ondansetron 4 mg was given. Time to the administration of rescue analgesia and the total dose of fentanyl over 24 hours were recorded. Time of regression of anaesthesia (the point at which the cephalad level of sensory anaesthesia receded two spinal segments) and the times to full recovery of sensory and motor block were also noted. Intraoperative and postoperative data were assessed by an observer who was unaware of the treatment allocation.

All the anaesthetists involved in drug preparation within the intraoperative and postoperative data collection periods were different so as to maintain the blinded nature of the study. The data were decoded at the end of the study and analysed statistically.

Statistics

Based on a preliminary study at the department, a 20% reduction in total fentanyl requirements from the baseline was considered to be clinically significant. It had been calculated that, to achieve a power of 80% and an α value of 0.05, 25 patients per group were needed. The one-way ANOVA (analysis of variance) test was used to compare the groups for demographic data, time of two-segment sensory regression, time of complete regression of sensory and motor block, time of rescue analgesia, total dose of fentanyl required, analgesic consumption at different time intervals and haemodynamic data.

The independent samples t-test was used for the comparisons between two groups. The χ^2 test was used for the analysis of the highest level of sensory block, maximum Bromage scale and side-effects. The Mann-Whitney test was employed for comparison between two groups, and the Kruskal-Wallis test for the time taken to achieve a T10 sensory level, total analgesic consumption over 24 hours and maximum pain scores. A p-value of less than 0.05 was considered statistically significant.

Results

There were no significant differences in patient characteristics or duration of surgery between groups (Table I). Two patients in group I and three patients in group III did not complete the study as they were administered general anaesthesia after 45 minutes of the start of surgery because of early block regression. Data from these patients were excluded from further analysis. There were no significant differences in the time of onset of sensory and motor block between the study groups (Table II). Vital signs were stable throughout the operation and there were no differences between patients in mean arterial pressure and pulse rate (data not shown).

The time to first rescue analgesia and fentanyl consumption in the postoperative 24-hour period showed no significant difference between the control and the adenosine groups (Table III). There were no significant differences in VAS pain scores (Figure 1). The time taken for complete regression of sensory block was comparable in all groups, although using ANOVA, the time taken for complete regression of motor block was significantly different between the groups (p=0.010; Figure 2). Inter-group comparison showed a statistically significant difference in regression of motor block between groups I and II, as well as between groups II and III, although groups I and III were comparable (Table III). Side-effects were observed in the form of lumbar pain and headache (Table IV). Lumbar pain was found to be statistically significant at the zero time point in all three groups (p=0.03). Eleven patients in group II had lumbar

Table I: Patient characterstics and duration of surgery. Values are mean ± standard deviation (range)

	Number of patients	Age (years)	Weight (kg)	Height (cm)	Duration of surgery (minutes)
Group I	25	49.56±8.02 (30-60)	49.76±9.81 (32-70)	155.64±2.98 (152-162)	100.00±19.71 (60-140)
Group II	25	51.56±7.62 (35-65)	49.32±8.75 (36-80)	156.56±3.63 (152-165)	97.60±23.05 (55-140)
Group III	25	51.36±7.63 (40-60)	50.88±7.17 (40-68)	155.12±2.65 (152-161)	106.55±32.30 (47-180)

Table II: Onset and characteristics of spinal block. Values are mean ± standard deviation (range)

|	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)	p-value
Time to achieve T10 sensory level (minutes)	3.74±2.80	2.60±1.44	2.82±1.94	0.236
[a]N_{MBS} at 1 minute	0	2	1	0.156
N_{MBS} at 5 minutes	4	15	14	0.240
N_{MBS} at 10 minutes	18	20	18	0.690

a = Number of patients achieving maximum Bromage scale

Table III: Regression characteristics of spinal block and postoperative analgesia

|	Group I (n = 23)	Group II (n =25)	Group III (n = 22)	p value
Time of two-segment sensory regression (minutes)	82.83±22.75	79.88±25.23	89.36±25.31	0.408
Time of complete regression of motor block (minutes)	206.74±38.83[a]	175.40±50.019[b]	212.05±39.97	0.010
Time of complete regression of sensory block (minutes) Duration of spinal anaesthesia (range)	229.57±40.08 (155-310)	232.60±78.03 (120-425)	237.59±36.83 (180-310)	0.889
Time of first rescue analgesia (minutes) (range)	129.57±49.92 (35- 220)	177.92±139.44 (45-780)	144.32±59.21 (30- 271)	0.195
Total dose of fentanyl required (μg) (range)	369.13±143.52 (60-890)	323.80±129.82 (0-600)	308.64±114.94 (140-520)	0.297

[a] p= 0.020 group I vs group II
[b] p = 0.009 group II vs group III

pain at zero hour as compared to four and three patients in groups I and III respectively. Sedation was noticed in 16 patients in group I, 11 patients in group II and 14 patients in group III. The difference was statistically significant at the second postoperative hour (p=0.015), when 14 patients in group I and 10 in group III experienced sedation, while only five patients in group II were sedated. The difference was again statistically significant at the fourth postoperative hour (p=0.039), when nine patients in group I and six patients in group III were under sedation, while only two patients in group II were sedated.
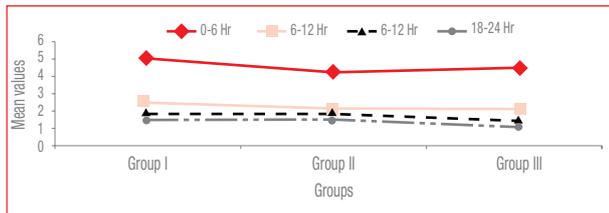
	0-6 Hr	6-12 Hr	6-12 Hr	18-24 Hr
Group I	4.91	2.3	1.91	1.52
Group II	4.12	2.16	1.8	1.48
Group III	4.45	2.09	1.45	1.09

Figure 1: Maximum pain scores over 24 hours. No significant difference in visual analogue scale pain scores
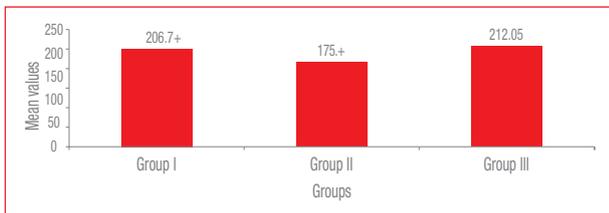
Group I	205.74	4	155.64	100
Group II	175.4	2	156.56	97.6
Group III	212.05	3	155.12	106.55

Figure 2: Time of complete regression of motor block (minutes). Statistical significance was recorded between groups I and II, and between groups II and III. No statistically significant difference was seen between groups I and III.

Table IV: Side-effects and complications

	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)
Sedation	16	11	14
Lumbar pain	15	15	12
Headache	0	2	1
Respiratory depression	0	0	0
Nausea and vomiting	13	9	13

Discussion

The present randomised, double-blind, placebo-controlled study in patients undergoing vaginal hysterectomy demonstrates that intrathecal administration of 500 μg or 1 000 μg of adenosine as an adjuvant to 0.5% hyperbaric bupivacaine in spinal anaesthesia does not affect the duration of pain relief and the postoperative analgesic requirement. There is no significant difference in the time to rescue analgesic, VAS scores and total fentanyl consumption among the groups. It neither hastens the onset of sensory and motor block, nor does it prolong the duration of spinal anaesthesia, although its usage hastens the regression of motor block.

Intrathecal injection of an adenosine agonist was first tested for anti-nociception in humans in 1995.[15] Intrathecal adenosine itself was first studied after preclinical safety testing by Sollevi et al in 1998,[16] and by Eisenach et al in 2002.[17-19] These trials suggested that intrathecal adenosine or its analogues failed to reduce acute pain in humans, although they reduce areas of hypersensitivity induced with topical irritants. Adenosine receptors have their highest concentration in the substantia gelatinosa in the dorsal column of the spinal cord, primarily at intrinsic neurons and primary afferents.[15]

Intrathecal adenosine has been studied in various clinical trials in doses ranging from 0.5 mg to 2.0 mg. Eisenach et al observed that a dose of 2 mg was associated with more side-effects. In addition, he suggested that lower doses of intrathecal adenosine need to be investigated further. Hence, we chose 500 μg and 1 000 μg in our study. A phase I clinical safety trial in healthy humans concluded that intrathecal adenosine in doses of 1 000 μg lacked adverse

effects and a dose of 500 µg was reported to be ineffective in relieving postoperative pain, but we decided to include 500 µg dose in our study as we were adding it to bupivacaine, which could have hastened its spread on receptors.[16]

Adenosine did not enhance the effect of bupivacaine in our study, which is in contrast to results by Apan et al where the use of adenosine was found to extend the duration of analgesia in brachial plexus block.[20] The results are also in contrast to a study where adenosine, given as intraoperative infusion, reduced the consumption of isoflurane by 50-60% during surgery and postoperative analgesics by 20%.[8] The fact that intravenously infused but not intrathecally injected adenosine could produce analgesia after visceral surgery suggests that lumbar spinal mechanisms may not be primarily responsible for the anti-nociceptive effect. Furthermore, the dose requirement may be different between experimental pain, where there is no continuous nociceptive input, and acute perioperative pain, with a massive afferent input. Adenosine also exerts well-known anti-inflammatory effects. Therefore, a peripheral anti-inflammatory mechanism could be a plausible mechanism of action of intravenously infused adenosine.

There was no significant difference in the onset times of sensory and motor block, indicating that the addition of adenosine did not hamper the binding of bupivacaine to nerve roots in the cerebrospinal fluid. The difference observed in motor block regression could be due to the focal vasodilatation caused by intrathecal adenosine, resulting in increased systemic absorption and thereby enhancing the metabolism of bupivacaine, leading to faster regression of motor blockade. The fact that adenosine did not enhance the regression of sensory block remains unexplained. Recorded side-effects included transient lumbar pain and headache, similar to the observations of Eisenach et al and Rane et al.[16,17] These could be explained by the vasodilatory effect of adenosine.

Conclusion

Intrathecal adenosine does not affect the duration of pain relief and the postoperative analgesic requirement when administered with hyperbaric bupivacaine. It also does not enhance the onset and duration of sensory and motor blockade of 0.5% hyperbaric bupivacaine. It has nevertheless significantly hastened the regression of motor blockade. The use of 1 000 µg intrathecal adenosine was associated with a higher incidence of lumbar pain than 500 µg adenosine. While the literature supports the role of intrathecal adenosine to relieve experimental and neuropathic pain, the efficacy of this drug to relieve postoperative pain still remains unproven. The lack of efficacy of intrathecal adenosine might be due to diffusion factors, where the penetration of adenosine into spinal cord is inadequate in an intact nervous system. Adenosine analogues with better tissue penetration should be studied in future to increase the drug concentration at the potential site of action.

Declarations

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