Original Research Article

Indian Journal of Anesthesia and Analgesia
Volume 7 Number 5, September – October 2020
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.7520.28

Adenosine as Perioperative Analgesia as an Adjuvent: A Comparative Study

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How to cite this article:
B Venkateswara Rao, G Srinivas Rao. Adenosine as Perioperative Anlgesia as an Adjuvent: A Comparative Study. Indian J Anesth Analg. 2020;7(5):1069–1074.

Abstract

Introduction: Painis a conscious experience that result from brain activity in response to a various stimulus and engages the sensory, emotional and cognitive process of the brain. Pain can be classified based on pain physiology, intensity, temporal characteristics, type of tissue affected, and syndrome.

Aims: A comparing adenosine as a perioperative analgesic as an adjuvant.

Materials and Methods: It is a randomised double-blind and controlled comparative study was conducted in fifty adult patients scheduled for various procedures under general anaesthesia. The patients in the age group of 25–50 years were taken for the study. Adenosine was compared with opioid (fentanyl) analgesia. The study involves n=25 study group n=25 control group.

Results: Control group received opioid analgesia injection fentanyl 2mcg\kg body weight started after intubation. The mean duration of surgery in both groups ranged between 75–90 mins.In comparision perioperative infusion of adenosine showed statistically significant stabilisation of hemodynamics intraoperatively and postoperatively over the control group. The VAS scoring suggested that adenosine group carried a good analgesic effect intraoperatively and postoperatively in comparison with control group.There are no significant side effects in adenosine group in comparison with control group.

Conclusion: The observation suggested that cumulative effect of adenosine infusion carried a good analgesic effect and hemodynamic stabilization in postoperative period. In post operative period patients who received adenosine not required any opiod or analgesic supplementation.

Keywords: Adenosine; Fentanyl; General anesthesia.

Introduction

An unpleasant sensory and emotional experience associated with actual or potential tissue damage or describes in terms of such damage. Pain is subjective, each individual learns the meaning of the word "pain" through experiences related to injury in early life. Biologists recognize that those stimuli or illness that cause pain are likely to damage the tissue. Accordingly pain is an experience we associate with actual or potential tissue damage. Pain is always unpleasant and therefore an emotional experience. Nociception is the process by which information about a various stimulus is conveyed to the brain. It is the total sum of neural activity that occupy prior to the cognitive process that enable humans to identify a sensation as pain. Nociception is necessary but not sufficient for the experience of pain. Perception is the process by which various event is recognized as pain by

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a conscious person. Multiple area of the brain is involved. There is no location where perception occur, although major defining component of pain are attributed to processes that place in specific areas of the brain. For example the sensory-discriminative component is the result of activity in the somatosensory and insularcortex, which allows the person to identify the type, intensity and bodily location of various event. The affective-emotional response to the various stimulus is mediated by the limbic systems.

However, the occurrence of severe pain on emergence from anesthesia and typical opioid-related side effects have been reported in the postoperative period.[1,2] Adenosine, a naturally occurring nucleoside recipe with potent sympatholytic properties, has been reported to potentiate the sedative effect of midazolam and to reduce the requirement for isoflurane and postoperative opioid analgesics.[3] Authors suggested that a perioperative adenosine infusion of 70–130 g. kg^{-1} min^{-1} could replace opioid wardship during isoflurane and nitrous oxide (N2O) anesthesia. Despite its extremely short plasma suppuration half-life (less than 10 s), preliminary studies reported that adenosine possesses long-lasting sympatholytic and analgesic-like effects.[4] The primary objective of the study was to compare Adenosine as a perioperative analgesic as an adjuvant effects.

Materials and Methods

It is a randomised double-blind and controlled comparative study conducted in fifty adult patients scheduled for various procedures under general anaesthesia, in ASA Grade-1 physical status, after Hospital ethical committee approval and informed consent from all patients. The patients in the age group of 25–50 years were taken for the study. The study was taken out only in surgeries lasting for not more than 75 mins.

Patients underwent Gynecological Procedures like Total Abdominal Hysterectomy, Staging Laparatomy for various clinical conditions. All the patients were assessed clinically preoperatively and presence of any medical disorder and history of drug intake was ruled out. Patients with H/O chest pain/palpitations/syncope, H/O Respiratory problems, and Hepatic or Renal problems were excluded from the study. Patients with the base line heart rate <60 beats per minute, base line systolic blood pressure <100mm Hg, ECG abnormalities were excluded from the study. Patients in whom intubation was thought to be difficult were excluded from the study. All the patients underwent the following investigations, namely complete urine analysis, haemogram, blood chemistry, x-ray chest a pre-operative ECG and 2D ECHO and cardiology evaluation.Thepatients were randomly allocated to two Groups Group-1 and Group-2 (having 25 patients in each group).

Group-1: Control

Comprising of 25 patients. This group did not receive Adenosine.

Group-2: Study

Comprising of 25 patients, who received Adenosine 80mcg/kg/min infusion at a rate of 6–8 ml/min 10 min after induction.

The premedication, induction agent and muscle relaxant to facilitate were standardized for both the groups. Intravenous cannulation was done with 18G cannula after shifting the patient into the waiting area of the operation theatre, and connected to a drip of ringer lactate solution. Premedication with Glycopyrrolate 5mcg/kg body weight Ondansetron 0.1mg/kg body weight were given slowly intravenously, 15 minutes before induction. Patient was connected to non-invasive blood pressure monitors, pulse oximeter probe and electrocardiographic leads. All patients were pre -oxygenated with 100% oxygen for 3 minutes.

The patient was induced by Thiopentone sodium (5mg/kg body weight). Intubation was facilitated by using Suxamethonium 2 mg/kg body weight. The lungs were ventilated with 100% oxygen for 90 seconds. Intubation was achieved with an appropriate size oral cuffed, portex endotracheal tube by the aid of Macintosh laryngoscope blade. The time taken for intubation did not exceed 20 seconds. Anaesthesia was maintained with Vecuronium bromide 0.08mg/kg top-up doses;time bounded doses were given for every 20 min inhalation agent used was isoflurane in range of 0.5% to 1% and intermittent positive pressure ventilation with nitrous oxide and oxygen in the ratio of 66%: 33% using circle absorber system connected to the datexmeda aneasthesia work station. Surgery was not allowed to commence till the recordings were completed. Recordings were done at pre-induction, post intubation, then every 15 mins till end of surgery. Parameters monitored HR, SBP, DBP, MAP, Intraoperative fluid requirement were also given according to

protocol blood loss and urine output monitoring also done. At the end of the surgery, neuromuscular blockade was reversed with Neostigmine (0.05mg/kg) Glycopyrrolate (0.08mg/kg). All the patients were followed in the post-operative period of 6 hrs for hemodynamicsadaquet analgesia. There is no evidence of any side effects of the adenosine or fentanel were seen in post-operative period in the comparison of both groups.

The parameters recorded were Heart Rate, Systolic Blood Pressure, Diastolic Pressure, Mean Arterial Pressure and Visual Analog Scores (post operatively).

The recordings were noted at various intervals as detailed below, from the study conducted Pre-operatively i.e. at pre-anaesthestic evaluation, Pre-induction i.e. after premedication, After induction, At laryngoscopy and intubation, Every 15 minute after intubation till the end of surgery andPost operatively for 6 hrs. Parameters monitored were HR, SBP DBP MAP VAS.

Results

Fifty patients undergoing elective surgeries were selected for this study. Patients randomly divided into two groups of 25 patients each group.

Table 1: Demographic details in study.

Group	Age (in years)	Weight (in kgs)	P-Value
Study (n=25)	41.3	55.3	>0.05
Control (n=25	42.1	55.9	>0.05

Table 1 showing age weight distribution in both groups range for age was 25–50 yrs for both groups. Range for weight was 30–55 kg. There is no statistical significant difference in both groups.

Table 2 parameters are recorded at the preinduction time, intubation and 15 min after intubation has no statistically significant difference was observed between control and study group. (P> 0.05).

Parameters were recorded after 30 min, 45 min,60 min, 75 min and 90 min there is statistically significant difference was observed between control and study group. (P value < 0.05).

Table 3 parameters are recorded 1st hour, 2nd hour, 3rd hour, 4th hour, 5 th hour and 6th hour after extubation there is statistically significant difference was observed in all parameters between study group and control group (P value < 0.05).

Table 2: Parameter in preintubation and intubation at different time periods.

Parameters	Study (Mean)	Control (Mean)	P-Value
Preinduction time			
HR	85.04 ± 2.34	81.72	<0.05
SBP	122.8	165.6	<0.05
DBP	76	77.2	<0.05
MAP	91.36	90.9	<0.05
Intubation			
HR	113.6	110.04	<0.05
SBP	159.6	202.8	<0.05
DBP	101.12	91.2	<0.05
MAP	119.99	110.87	<0.05
15 mins after intubation			
HR	84.72	86.36	<0.05
SBP	116.76	128.4	<0.05
DBP	75.88	80.2	<0.05
MAP	90.016	96.77	<0.05
30 mins after intubation			
HR	78.44	85.92	<0.05
SBP	108.32	128.75	<0.05
DBP	72.24	77.4	<0.05
MAP	84.18	94.96	<0.05
45 mins after intubation			
HR	74.68	87.4	<0.05
SBP	107.32	131.72	<0.05
DBP	70.28	79.72	<0.05
MAP	82.58	97.21	<0.05
60 mins after intubation			
HR	76.12	96	<0.05
SBP	109.08	137.76	<0.05
DBP	72.24	84.72	<0.05
MAP	82.25	103.23	<0.05
75 mins after intubation			
HR	78.76	94.48	<0.05
SBP	109.4	135.2	<0.05
DBP	71.84	83.92	<0.05
MAP	84.19	100.89	<0.05
90 mins after intubation			
HR	78.44	85.92	<0.05
SBP	108.32	128.75	<0.05
DBP	72.24	77.4	<0.05
MAP	84.18	94.96	<0.05

P-Value- <0.05 is significant

Table 3: Post operative observation and after extubation at various time periods.

Parameter	Study	Control	P-value
1st hour after extubation			
HR	81.28	88.56	<0.05
SBP	111.52	128.8	<0.05
DBP	73.88	81.8	<0.05
MAP	86.07	96.7	<0.05
2nd hour after extubation			
HR	83.6	92.96	<0.05
SBP	117.8	132.72	<0.05
DBP	76.84	83.4	<0.05
MAP	91.08	99.62	<0.05
3rd hour after extubation			
HR	85.8	99.96	<0.05
SBP	123.16	137.92	<0.05
DBP	80.4	85.4	<0.05
MAP	95.5	102.5	<0.05
4th hour after extubation			
HR	92.4	105.8	<0.05
SBP	128.56	141.32	<0.05
DBP	83.6	88.76	<0.05
MAP	99.76	106.2	<0.05
5th hour after extubation			
HR	98.8	100.08	<0.05
SBP	135.72	138.2	<0.05
DBP	89.04	85.6	<0.05
MAP	106.12	102.4	<0.05
6th hour after extubation			
HR	107.8	93.36	<0.05
SBP	143.6	132.4	<0.05
DBP	91.68	82.84	<0.05
HR	107.8	93.36	<0.05

P-Value <0.05 is significant

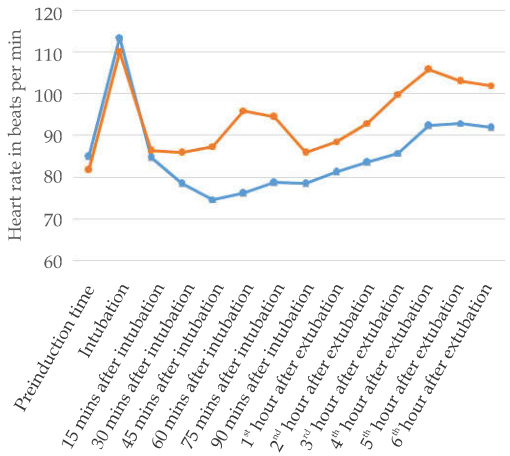

Fig. 1: Heart rate in various periods of study.

Heart rate is significant from 30 min after intubation till 6 th hour of extubation. (Fig. 1)

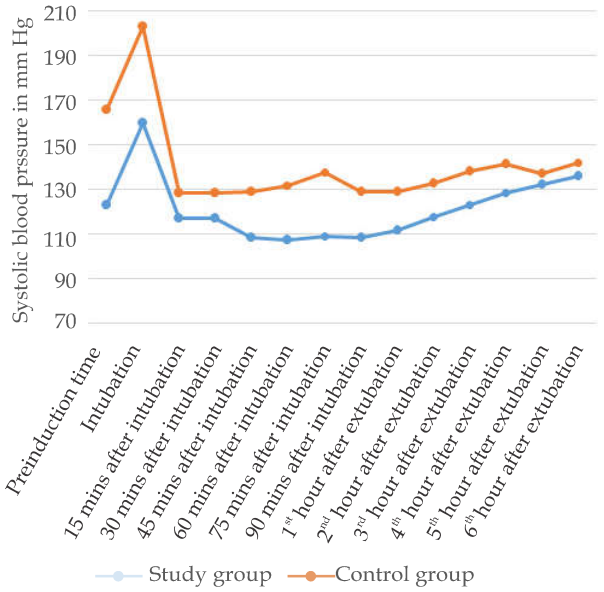

Fig. 2: Systolic blood pressure in various periods of study.

Systolic blood pressure is significant all over till 6 th hour of extubation. (Fig. 2).

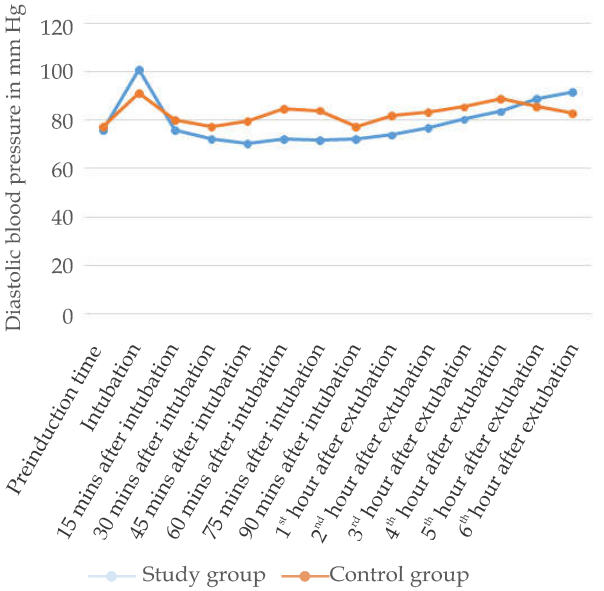

Fig. 3: Diastolic blood pressure in various periods of study.

Diastolic blood pressure is significant all over till 6th hour of extubation. (Fig. 3)

Table 4: VAS scores are recorded at 1–6 hrs in postoperative period.

Time periods	Study	Control
1st hr	0.35	5
2nd hr	0.56	6
3rd hr	2	6.6
4th hr	2.6	7.3
5th hr	3.2	6.8
6th hr	3.4	6

In Table 4 there is statistically significant difference was observed between study and control groups at initial four hrs.

Discussion

Acute pain is an expected out come after any kind of surgery. According one study approximately 80% of patients undergoing surgery experienced acute pain during postoperative period. Pain after surgery can impede recovery increase hospital stay increase health care costs affects patient's general activity and sleep despite increased focus on pain management and development of pain management guidelines, and the postoperative pain remains an important issue in the perioperative setting. Opioids remain the main stay for postoperative analgesia especially after major surgeries. However pain is a multifactorial phenomenon that may not be controlled adequately with opioid monotherapy and opioid use may be associated with dose related adverse effects such as respiratory depression, nausea vomiting, urinary retention, itching, and sedation.

To improve pain relief and reduce the incidence and severity of side effects a multi model approach to postoperative analgesia should be used.In our study we are investigated the effects of IV adenosine on anaesthetic requirements and post-operative recovery and analgesic effect in patients undergoing major surgical procedures under general anaesthesia.

Adenosine was compared with opioid (fentanyl) analgesia in a randomised double-blind and controlled comparative study. The study involves n=25 study group n=25 control group.The anaesthesia technique, drugs used in premedication, induction, intubation and maintenance and inhalational agent used were standardized for both groups. Study groupreceived adenosine 8mcg\kg\ min infusion started 10 mins after induction, after stabilization of heamodynamics. Control group received opioid analgesia injection fentanyl 2mcg/ kg body weight started after intubation. The mean duration of surgery in both groups ranged between 75–90 mins. Adenosine infusion was stopped immediately after completion surgery. In one study, patients received a perioperative infusion of adenosine adjusting the dose as needed to maintain acceptable hemodynamic stability. Infusion rates were also variable in the second study, ranging from 72 to 290 μg • kg^{-1} • min^{-1} for adenosine. In both studies, excellent hemodynamic stability was maintained intraoperatively by both drugs. In one study, the time to complete orientation was significantly faster with adenosine compared with remifentanil (mean ± sd: 6 ± 2 min vs 31 ± 12 min, $P < 0.05$). In this study, postoperative sedation and nausea were also significantly less in the adenosine group.[5,6,7]

In comparision perioperative infusion of adenosine showed statistically significant stabilization of hemodynamics intraoperatively and postoperatively over the control group. The VAS scoring suggested that adenosine group carried a good analgesic effect intraoperatively and postoperatively in comparison with control group. Fukunagaet al. (2003) also observed significantly reduced pain scores in their study with adenosine.[5]

There is no significant side effects in adenosine group in comparison with control group. The observation suggested that cumulative effect of adenosine infusion carried a good analytic effect and hemodynamic stabilization in postoperative period. In post-operative period patients who received adenosine not required any opiod or analgesic supplementation.

In this study involving females who underwent total abdominal hysterectomy 2 of 25 evaluable adenosine-treated pts. Reported one or more of the following: hematoma; fever;reoperation due to postoperative bleeding; due to surgical reasons.

1 of 25 adenosine treated pts. Experienced an adverse event: transient atrioventricular block II or transient decrease in systolic blood pressure due to accidental overdose. In who underwent surgery abdominal hysterectomy and received IV adenosine 2 pts. Experienced an adverse event ASHeadache (adenosine), faintness (adenosine), palpitation/ tightness (adenosine), and itching.

Pts who underwent hysterectomy 1 of 25 pts in the adenosine group experienced sever bronchospasm shortly after ignition of infusion.

In Gan Tang J et al study 8 were usually moderate and well tolerated by most patients

(81 per cent). Extreme bronchospasm was the most significant incident recorded in seven cases. There were no deaths, so there were just one cases of myocardial infarction so pulmonary edema each. Transient AV block existed in 8 percent of patients and was usually overcome in the adenosine infusion without any improvement.

There was no continuous series of AV block. Adenocard's safety profile is very similar to the one described for Adenoscan.

Owing to the extremely short adenosine half-life of whole blood (< 10 s) (12,13), concerns about the treatment of cardiovascular side effects are minimised. However, it is important to note that in nonsurgical use the safety of adenosine may not reflect its protection during the perioperative phase.

Like nonchirurgical application, there can be a variety of drug-to-drug reactions between adenosine and inhaled anesthetics and opioids that can aggravate adenosine's hemodynamic effects.

Furthermore, with enhanced bronchotracheal stimulation during the perioperative phase, the bronchoconstriction risk could be greater than in a non-surgical population.

Conclusion

Adenosine is Good Analgesia without Sedation, Excellent Controllability, Stimulates Breathing, Mild Hemodynamic Effects, No Postoperative Hyperalgesia, Treats Pulmonary Hypertensionand May be used in Opiate Addicts.

Adenosine appears to demonstrate opiod-sparing, anesthetic-sparing, and analgesic properties Dose finding clinical studies are warranted to establish the optimal dose for achieving a balance between efficacy and side effects profile for adenosine use in the perioperative setting.

References

1. Sawynok J, Liu XJ. Adenosine in the spinal cord and periphery: release and regulation of pain. Prog Neurobiol. 2003;69(5):313–340.
2. Cronstein BN. Adenosine, an endogenous anti-inflammatory agent. J ApplPhysiol (1985). 1994;76(1):5–13.
3. Bours, M J, Swennen, EL, Di Virgilio, F, Cronstein, BN & Dagnelie, PC Adenosine 5′-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. 2006: Pharmacol. Ther. 112, 358–404 .
4. Burnstock G. Physiology and pathophysiology of purinergic neurotransmission Physiol Rev. 2007;87(2):659–797.
5. Fukunaga AF, Alexander GE, Stark CW. Characterization of the analgesic actions of adenosine: comparison of adenosine and remifentanil infusions in patients undergoing major surgical procedures. Pain 2003;101:129–38.
6. Rane K, Sollevi A, Segerdahl M. Intrathecal adenosine administration in abdominal hysterectomy lacks analgesic effect. Acta AnaesthesiolSc and 2000;44:868–72.
7. Zarate E, Sa Rego MM, White PF, Duffy L, Shearer VE, Griffin JD, Whitten CW. Comparison of adenosine and remifentanil infusions as adjuvants to desflurane anesthesia. Anesthesiology 1999;90:956–63.
8. Gan, Tong J, MB, FRCA, FFARCSI; Habib, Ashraf S, MB, FRCA Adenosine as a Non-Opioid Analgesic in the Perioperative Setting, Anesthesia & Analgesia: August 2007 - Volume 105 - Issue 2 - p 487–494 doi:
9. Package insert for Adenocard®. Available at: www.fujisawa.com/medinfo/pi/pi_page_ac.htm. Accessed Dec. 7, 2006.
10. Package insert for Adenoscan®. Available at: www.fujisawa.com/medinfo/pi/pi_main_as.htm. Accessed Dec. 7, 2006.