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Combination of Adenosine with Prilocaine and Lignocaine for Brachial Plexus Block Does not Prolong Postoperative Analgesia

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SUMMARY

Adenosine analogues have been used by subarachnoid injection for the treatment of inflammatory and neuropathic pain. There are no data on the use of adenosine in peripheral nerve blocks. The aim of the present study was to determine the analgesic efficacy of adenosine in combination with a local anaesthetic solution for brachial plexus (BP) block.

With local ethics committee approval, 50 consenting adult patients undergoing upper limb surgery were enrolled in this double-blind, prospective, randomized study. Patients with a history of bronchospastic disease were excluded. Patients were instructed not to take theophylline-containing drugs and beverages for at least one day before surgery or on the first postoperative day. A supraclavicular BP block was performed by injecting a mixture totalling 35 ml made up of prilocaine 1% 10 ml and lignocaine 2% 20 ml with adrenaline 1:200 000, and adenosine 10 mg in 5 ml saline (Group 1) or 5 ml saline (Group 2) as a placebo control group. Postoperative analgesia was assessed by time to first rescue analgesia, analgesic consumption in the first 24 hours, and VAS at rest at 4, 8, 12, 16, 20 and 24 hours. Side-effects were also noted.

Vital signs were stable in both groups throughout the operation. There were no significant differences between the groups in onset of motor and sensory block. Time to first pain sensation from block was not significantly longer in the adenosine group (379±336 min) compared with controls (304±249 min, mean±SD, P=0.14). Time to first analgesic requirements and analgesic consumption in the first 24 hours were also similar in both study groups.

In the present study, the addition of adenosine to local anaesthetic in brachial plexus block did not significantly extend the duration of analgesia.

Key Words: REGIONAL ANAESTHESIA: brachial plexus block. POSTOPERATIVE ANALGESIA: adenosine

Adenosine is a purine, purines being endogenous compounds with many biological effects[1]. Adenosine has recently been used in the treatment of various pain states. When administered systemically, intracerebroventricularly and intrathecally (IT), adenosine receptor agonists have been demonstrated to induce antinociception[2,3]. At least two subtypes of adenosine receptors are involved in pain modulation and antiallodynic effects are mediated through activation of A1 adenosine receptors[4]. Animal studies suggested possible involvement of adenosine receptor agonists with opioid agonists and other biologically active compounds in pain modulation. Pretreatment with adenosine analogues attenuated substance P-induced nociception and this effect was not reversed by naloxone[5]. On the other hand, the nonspecific adenosine receptor antagonist, theophylline, reversed IT morphine-induced antinociception[6]. Concurrent administration of adenosine with neostigmine showed a synergistic effect, and adenosine with clonidine additively attenuated allodynia in a postoperative hypersensitivity model[7].

There are few clinical reports of the role of adenosine in perioperative or neuropathic pain. Adenosine receptor agonists have been effective in patients complaining of neuropathic symptoms[8-10]. Adenosine infusion caused a reduction in additional anaesthetic requirement and postoperative analgesic consumption[11,12] and hyperaesthesia induced by neuropathic pain[13]. Various drugs have been combined with local

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anaesthetic drugs for extending the analgesic period in brachial plexus anaesthesia[14]. There is no information regarding the effect of adenosine on postoperative pain when used for peripheral nerve block. The present investigation aimed to compare the quality of block and duration of postoperative analgesia of either a combination of adenosine or placebo with local anaesthetic for brachial plexus block.

METHODS

After institutional ethics committee approval and patient consent, 50 ASA I-II patients were enrolled in a double-blind, prospective, randomized study. Patients were included if they were undergoing upper limb surgery suitable for supraclavicular brachial plexus block. Exclusion criteria included chronic airway limitation and concurrent theophylline therapy. Randomization was performed by closed envelopes chosen by the patient prior to the procedure. Patients were premedicated with intramuscular diazepam 10 mg 30 minutes before blockade. Routine anaesthetic monitoring included continuous lead II electrocardiogram, pulse oximetry and noninvasive arterial blood pressure measurement every five minutes. Venous access was with an 18 gauge cannula on the dorsum of the contralateral hand. Brachial plexus block was performed as a modified supraclavicular technique, surface landmarks of which are described elsewhere[15]. Coded syringes containing the study solution were supplied by the Pharmacy Department. Adenosine was sourced from Sigma chemicals (St Louis, MO, U.S.A.), weighed and packaged in 5 ml syringes and sterilized by ethylene oxide. A short-bevelled 5 cm stimulating needle (Stimuplex®, B.Braun, Melsungen, Germany) was used for the block. Stimulation was at 2 Hz with an impulse duration of 0.1 ms and considered satisfactory for injection if muscle twitches at elbow, wrist or fingers were present at less than 0.5 mA. Brachial plexus block was performed with a mixture of prilocaine 1% 10 ml and lignocaine 2% 20 ml with adrenaline 5 μg/ml to which 5 ml of 0.9% saline was added with adenosine 10 mg in Group 1 and no additive (placebo) in Group 2. Quality of motor block was assessed every 5 minutes by a modified Bromage scale that evaluated the ability to perform voluntary movements and the strength of elbow and hand movements. Pain sensation to pinprick was assessed in ulnar, radial and median nerve distributions on the hand. Surgery commenced when the block was adequate. Quality of analgesia was graded as good (no supplementary local anaesthetic injection required), satisfactory (supplementary local anaesthetic injection required) and failed (general anaesthesia required). If systolic blood pressure was $<$90 mmHg, or when the decrease of baseline mean arterial pressure was noted to be more than 20%, ephedrine 5 mg was administered IV. Bradycardia was defined as a decrease in heart rate to $<$60 bpm, and atropine (0.5 mg) IV was given if the heart rate was $<$45 bpm.

Time to first complaint of pain and analgesic requirement was noted in the postoperative period. Pain was assessed using a Visual Analogue Scale (VAS). The device consisted of a 100 mm sliding plastic measure graded from 0 (No pain) to 100 mm (Worst imaginable pain). The patient's VAS was assessed by a blinded observer at the end of the operation and every four hours for 24 hours. Postoperative "rescue" analgesia was diclofenac 75 mg IV and total analgesic consumption was assessed for 24 hours postoperatively. Follow-up neurological examination was performed one week after the operation. Statistical analyses were performed using Chi square, ANOVA, Kruskal-Wallis and Mann-Whitney U tests as appropriate. Data were expressed as mean$\pm$ standard deviation (mean$\pm$SD) or median (Range). A P value $<$0.05 was considered significant.

RESULTS

There were no significant differences in patient characteristics or duration of surgery (Table 1), and the distribution of types of surgery was also similar in the two groups (Table 2). One patient in Group 1 had a failed block and general anaesthesia was administered. Data from this patient was excluded from further analyses. There were no significant differences in onset of sensory and motor block between study groups (Table 3). Vital signs were stable throughout the operation and there were no differences between patients in mean arterial pressure and pulse rate (data not shown). No patient required treatment with ephedrine or atropine. Most patients were operated on under tourniquet (94%) and none experienced intraoperative discomfort or pain. The time to first pain sensation and first rescue analgesic and analgesic consumption in the postoperative 24h period (diclofenac sodium, mg) showed no significant difference between control and adenosine groups (Table 3). Three patients from the control group and four patients from the adenosine group did not require any analgesic in the first 24 hours. There were no significant differences in VAS values in the first 24 hour period (Figure 1). Side-effects were negligible. One patient in the adenosine group complained of headache and one patient in the control group developed an itch.

TABLE 1
Patient characteristics and duration of surgery

	Group 1 (n=25)	Group 2 (n=25)
Age (y)	38±13	41±13
Weight (kg)	74±13	71±11
Height (cm)	165±9	162±8
Sex (M/F)	7/18	5/20
ASA physical status (I/II)	24/1	24/1
Surgery time (min)	67±42	62±41

No significant difference between groups. Values are mean±SD. ASA=American Society of Anesthesiologists.

TABLE 2
Types of surgery

	Group 1 (n=25)	Group 2 (n=25)
CCT release	8	10
Trigger finger	2	3
Soft tissue excisions	2	6
Skin flaps and grafting	5	3
Application of external fixateurs	3	1
ORIF	5	2

CCT=Carpal and cubital tunnel, ORIF=Open Reduction and Internal Fixation.

TABLE 3
Characteristics of supraclavicular brachial plexus block and postoperative analgesic data

	Group 1 (n=25)	Group 2 (n=25)
Onset time of sensory block (min)	8.7±4	9.5±5
Time to complete motor block (min)	25±7	28±10
Quality of sensory block		
Good	21	21
Satisfactory	3	4
Failed	1	0
FPS from block (min)	260 (120-1440)[a]	240 (120-1440)
FRA from block (min)	460 (180-1440)[a]	350 (210-1440)
Diclofenac mg/24h	106±62[a]	103±53

No significant difference between groups. Values are mean±SD and median (Range). FPS=First pain sensation, FRA=First rescue analgesic, [a]: n=24.

DISCUSSION

As far as we know, this is the first study of the possible role of adenosine in post-surgical pain when administered for peripheral nerve block in combination with local anaesthetic mixture. In the present study, there was no significant effect on postoperative pain of adenosine added to local anaesthetic-based brachial plexus block. A much larger study might detect a small but statistically significant difference created by the addition of adenosine to local anaesthetics for peripheral nerve block. Given the small absolute difference in effect that we detected and the large within-group variability, we believe that our results indicate that differences that might be detected by larger studies are unlikely to be of clinical significance.

Administration in the subarachnoid space has been reported to increase the adenosine concentration up to 1000-fold[10]. The dose of adenosine in the present study was 20-fold more than the minimum dose used in the subarachnoid study. It seems likely that this dose should be sufficient for neuronal uptake and

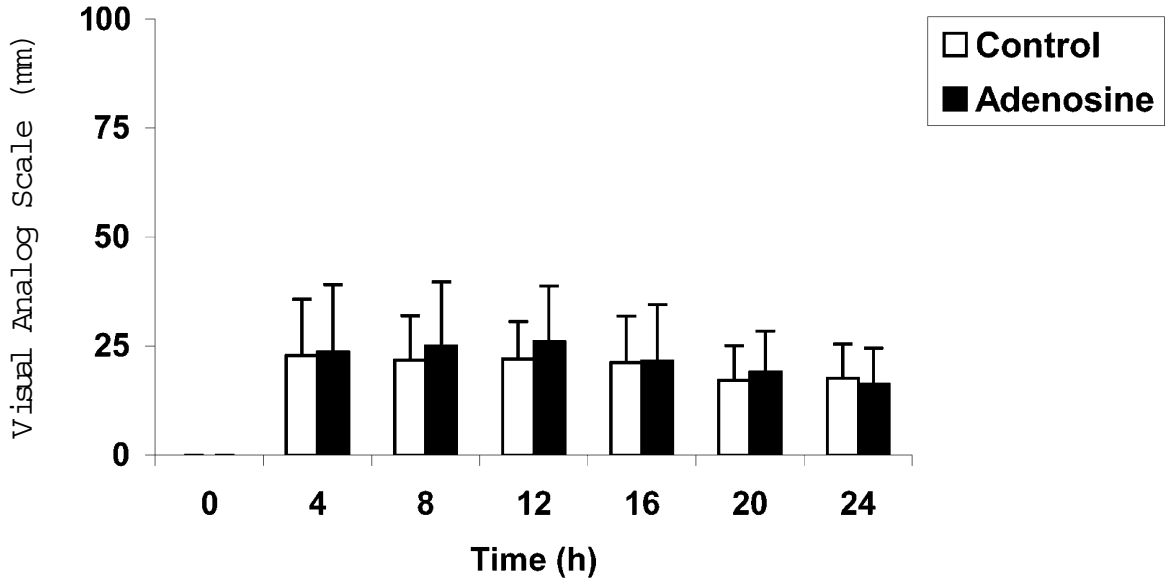

FIGURE 1: Visual analogue scale values during the first 24 hours in the postoperative period.

modulation of pain in peripheral nerves should such an effect exist. The pharmacokinetics and dynamics of adenosine may differ according to the site of injection.

A supra-additive interaction between adenosine A1 receptor agonist R-phenylisopropyladenosine (R-PIA) and morphine, reduced mechanical allodynia-like behaviour in rats with chronic spinal cord injury[16]. Intrathecal adenosine administration in patients with chronic neuropathic pain reduced spontaneous and tactile pain, and the area of hyperaesthesia for a mean of 24 hours[10]. Adenosine administration via the same route however, did not influence perioperative pain and postoperative analgesic consumption[17]. On the contrary, adenosine infusion reduced perioperative anaesthetic requirement and total amount of analgesic used in the postoperative period by using the same surgical model[12,13]. Adenosine infusion consistently reduced anaesthetic requirements in animal investigations[18]. Adenosine infusion was found to be effective in patients with neuropathic pain in attenuating spontaneous and stimulus evoked pain[13].

Adenosine did not relieve post-surgical pain via application to peripheral nerves (brachial plexus block) in the present study. Adenosine via infusion did reduce experimentally induced ischaemic pain (tourniquet on upper arm)[19]. Interestingly, Rane et al[10] recently demonstrated that IT adenosine treatment also reduced tourniquet-induced pain in the arm and suggested that adenosine was able to reach at least cervical segments. On the other hand, this group concluded that the inefficiency of IT adenosine pretreatment was due to the failure to reach the effect sites in the central nervous system[17]. This conclusion was at odds with the long term remission observed in a patient treated with IT adenosine A1 receptor agonist R-PIA[8].

Apparently conflicting results from various studies suggest that there are basic differences in the role of adenosine in pain modulation according to the site of administration. Attenuation at supraspinal level of sensitization induced by acute pain such as surgical incision or ischaemia might explain the efficacy of adenosine infusions. Adenosine administration in the subarachnoid space or to a compartment close to the nerves, as in the present study, failed to reduce the pain induced by the same mechanisms.

The efficacy of adenosine may also vary with the nature of the pain. Adenosine may be effective at a spinal level for chronic noxious stimuli rather than acute perioperative pain. In a recent study on rodent nerve cell cultures, adenosine receptor subtypes had regional differences in the central nervous system according to adenylate cyclase activity[20]. Pain organization at the supraspinal level may differ and adenosine may be effective at as yet undefined central nervous system receptors. Continuous infusion of adenosine may act at these sites. Rearrangement of synaptic transmission may occur with chronic noxious stimuli at spinal cord level and adenosine receptors may be activated in human subjects. Thus, IT adenosine administration was beneficial in a patient with neuropathic pain. This may also be consistent with the limited role of opioid administration for neuropathic pain syndromes[21]. Observations on adenosine agonists, which attenuated substance P and N-methyl-D-aspartate-induced nociceptive behaviour in mice, may further support these conclusions[22]. When rank order of potencies of adenosine agonists and opioid receptors were compared, adenosine agonists additively interact with the mu receptor and synergism was observed with delta and kappa receptor agonists in mice[23].

Implementation of treatment earlier in the pathogenesis of the neuropathic response may explain discrepancies between animal studies and clinical observations. The reasons why opioid agonists are insufficient in neuropathic pain and adenosine ineffective for surgical pain by IT or peripheral nerve block are still conjectural. Selective desensitization or synaptic rearrangement of specific receptor sites for each drug may partially explain these phenomena.

In contrast to injection into the subarachnoid space, adenosine administration for BP block did not produce pain or dullness during injection, possibly due to the combination with local anaesthetics[9].

In conclusion, combination of adenosine with local anaesthetics failed to significantly extend the duration of analgesia in brachial plexus block, even when relatively short acting local anaesthetics were used. The role of adenosine in neuropathic pain syndromes and continuous infusion of adenosine in acute pain remain potentially fruitful areas for investigation.

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