

Ultrasound-guided continuous infraclavicular brachial plexus block using bupivacaine alone or combined with adenosine for pain control in upper limb surgery

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ABSTRACT

Introduction: The infraclavicular brachial plexus block (ICB) is designed to deposit anesthetic high in the plexus, achieving anesthesia of the hand, forearm, elbow, and distal arm. Adenosine is a metabolic intermediate that is involved in nearly all aspects of cell function, including neurotransmission and signal transduction. This study was aimed to show whether addition of adenosine to bupivacaine in ultrasound-guided ICB had an analgesic effect. **Methods:** Sixty adult patients were divided into two equal groups, each group included 30 patients. Group I received infraclavicular bupivacaine 0.325% in a volume of 30 ml. Group II received 30 ml of 0.325% bupivacaine + 12 mg adenosine. The block was maintained with an infusion of 10 ml/h. The following parameters were assessed: Success rate, time of the sensory onset, motor block, visual analog scale (VAS), and amount of i.v. pethidine needed. **Results:** This study showed an analgesic effect of infraclavicular adenosine as evidenced by a statistically significant shorter mean time of onset of the sensory block (16 vs. 20 min, $P < 0.05$), lower mean VAS score over 48 h (1.7 vs. 2.7, $P < 0.05$), longer mean time of first parenteral analgesic requirement (299 vs. 255 min, $P < 0.05$), and lower mean total dose of pethidine needed over 48 h after surgery (25.5 vs. 56.6 mg, $P < 0.05$). All patients got successful infraclavicular block and recovered uneventfully without any sensory or motor deficit. **Conclusion:** Adenosine may provide valuable addition to the therapeutic options in anesthesia and pain management. Further research is required to figure out its exact role.

Key words: Adenosine, analgesia, infraclavicular block

INTRODUCTION

Infraclavicular brachial plexus block (ICB) is designed to deposit anesthetic high in the plexus, achieving anesthesia of the hand, forearm, elbow, and distal arm. The block meets the axillary and musculocutaneous nerves at the level of the cords before these nerves leave the brachial plexus sheath. In contrast to interscalene and supraclavicular blocks, the infraclavicular approach carries minor risks of intravertebral, intrathecal, or epidural injection, phrenic

nerve paralysis or stellate ganglion block. However, it carries the risk of pneumothorax, nerve injury, or hematoma.^[1-3] The use of ultrasound enhances the practitioners' ability to view the surrounding anatomy.^[3]

Adenosine triphosphate (ATP) and adenosine mediate many biological processes in the body as neurotransmission, transduction of signals, cardiac function, vasodilatation, and platelet function.^[4,5]

Both are released from variable cell types to interact with purinergic receptors present on the surface of the cells. Inside the body, ATP is metabolized rapidly to adenosine.^[6] Variable types of purinergic receptors mediate *in vivo* signal transmission by ATP and adenosine. These purinergic receptors determine the different and final effects induced by ATP and adenosine.^[7]

Adenosine has an important role in the central and

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peripheral mediation of pain. Adenosine A1, A2A, A2B, and A3 receptors were detected in the spinal cord. The A1 receptor plays an important role in spinal antinociception, whereas the role of the A2A, A2B, and A3 receptors is still vague. A2A and A3 receptors mediate pain transmission peripherally, whereas the A1 receptor seems to have a central antinociceptive effect. Analgesia was achieved in animals by raising the levels of extracellular adenosine through inhibition of adenosine kinase.^[8,9]

This study was aimed to determine the analgesic efficacy of adenosine in combination with a local anesthetic solution for ICB.

METHODS

This prospective, randomized, double-blinded study was carried out in Minoufiya University Hospital on 60 adult patients undergoing minor orthopedic surgeries in the hand and forearm after a written informed consent was obtained from the patients and institutional review board approval was obtained.

Careful history taking, thorough clinical examination and biochemical analysis, was performed to ensure that patients were ASA I or II physical status.

All patients underwent the ICB (the coracoid approach) by a continuous infusion. The patients were randomly allocated to receive bupivacaine ($n=30$) or bupivacaine + adenosine ($n=30$) by random numbers (Microsoft EXCEL). Randomization was done centrally by an independent statistician to ensure appropriate concealment. Allocation of study management was concealed from patients, primary investigators, and all coinvestigators until the release of the final statistical analysis. The placebo vs. adenosine mixture injectates were supplied by the pharmacy.

Exclusion criteria

The exclusion criteria are patient refusal, peripheral neuropathy, chronic pain, chronic analgesic use, coagulopathy, history of brachial plexus injury, known allergy to the study drugs, systemic infection, and sepsis at the site of injection or operations in the shoulder.

The patients were instructed to avoid taking adenosine antagonist as theophylline, other methylxanthines, and beverages such as coffee and tea the day before surgery and for 2 days postoperatively. In addition, the patients were instructed preoperatively in the use of the visual analogue scale for pain evaluation.

The technique

The patient was in the supine position with the head facing away from the side to be anesthetized. The premedication of the patient was 1–2 mg of midazolam i.v. In addition, 50–100 µg of fentanyl i.v. was administered just before insertion of the needle.^[10] This typically produced tranquil and analgesic patients for the procedure and no cases of respiratory depression were reported. Local injection of 4 ml lidocaine 1% was done at the puncture site. The patient was continuously monitored during the technique and thereafter (continuous ECG, pulse oxymetry, and noninvasive blood pressure).

Equipment

An ultrasound machine + 8–12 MHz probe was used. The ultrasound probe (8–12 MHz) of a Hewlett-Packard 77020A ultrasound monitor (Andover, MA, USA) was applied in the parasagittal plane close to the coracoid process and directed to best visualize the axillary artery.

A 10-cm long 18-G nontraumatic insulated needle (Plexolong; Pajunk, Geisingen, Germany) attached to a nerve stimulator was applied immediately next to the ultrasound probe at approximately 60–70° angle and in line with the longitudinal axis of the probe. The needle insertion angle was in parallel to the long axis of the probe to be capable of seeing the path of the needle on the ultrasound screen.

A nerve stimulator (Stimuplex®; Braun, Melsungen, Germany) was combined with the ultrasound to make sure that what is seen on the ultrasound screen reflects the brachial plexus. Initial stimulating current was 0.6–0.8 mA. Brachial plexus was reached at the depth of 6–8 cm. The stimulating current was then gradually decreased until the sought response was still present at 0.3 mA or less. Twitches from biceps muscle were not accepted, since the musculocutaneous branch may be outside the brachial sheath and the needle was redirected inferiorly and slightly medially to get stimulation of the median nerve. Stimulation of the axillary nerve (deltoid muscle twitch) was not accepted as the axillary nerve is often outside the brachial sheath at this level, and the needle was redirected more superiorly. Twitches from triceps, forearm, and hand muscles were accepted for the successful block.

The needle was withdrawn leaving the cannula. A 20-gauge multiperforated (epidural-type) catheter was inserted through the cannula. The cannula was withdrawn, leaving the catheter in place. The catheter was secured by sutures to the skin and covered with a bioocclusive dressing.

Aspiration through the catheter was performed to detect unintentional intravascular placement. A single test dose of 4 ml 1% lidocaine with epinephrine 5 µg ml⁻¹ was administered, followed by the loading dose of local anesthetic given incrementally. The injectate was 30 ml of 0.325% bupivacaine alone in group I or 30 ml of 0.325% bupivacaine + 12 mg adenosine in group II. The block was maintained with an infusion of 10 ml hr⁻¹ of local anesthetic solution with the same content and concentration as the initial injectate. The infusion was stopped 2 h after surgery. Adenosine injection (Adenocard[®]) was supplied as a sterile nonpyrogenic solution in normal saline; 6 mg 2 mL⁻¹ (3 mg mL⁻¹) in 2 mL (fill volume Ansyr[®] plastic disposable syringe), manufactured by Hospira, Inc., Lake Forest, IL 60045, USA. The 12 mg adenosine dose was used as it is a safe dose regarding the effect on hemodynamics if inadvertent intravascular injection occurred. Doses higher than 12 mg are not recommended.^[10] The pH of the injectate was 4.5 in both groups and the injectate had the same osmolarity and volume in both groups.

Attention was given to signs and symptoms of local anesthetic toxicity and catheter migration. Oral 1 g paracetamol tablet was given regularly every 6 h starting at 12 h postoperatively.

Parameters and recordings

- (i) Success rate: A block was considered successful only if all dermatomes of the brachial plexus (C5 to T1) were blocked by the original injection within 30 min. The block was considered incomplete if a supplemental injection was needed for complete anesthesia. The block was considered to have failed if a supplementary injection did not complete the anesthesia.
- (ii) Time of onset of the sensory block: Tested every 3 min until 30 min after injection of the local anesthetic.
- (iii) Motor block: It was assessed every 5 min until 30 min after giving the local anesthetic and graded as follows: Grade I = ability to flex and extend the forearm and was given a score of 1; Grade II = ability to flex or extend only the wrist and fingers and was given a score of 2; Grade III = ability to flex or extend only the fingers and was given a score of 3; Grade IV = inability to move the forearm, wrist, and fingers and was given a score of 4. The final total motor score (sum of all patients' motor scores in each group) was calculated.
- (iv) Pain scoring: The visual analog scale (VAS) for pain values on 10 cm line at 30 min, 2 h, 12 h, 24 h, 36 h, and 48 h postoperatively.
- (v) Time to first rescue analgesia.
- (vi) The amount of i.v. pethidine, according to the VAS, where patients received, rescue analgesic (pethidine

0.5 mg kg⁻¹ i.v.) when the VAS score was more than 40 mm or on patient demand.

- (vii) Complications from the drugs and technique (local anesthetic toxicity, pneumothorax, hypotension, bradycardia, etc).

The primary outcome measure was duration of analgesia. Secondary outcome measures were onset and duration of sensory block, pain scoring, motor blockade score, narcotic requirements, and any suspected adverse drug reactions.

Statistical analysis

Prior to the study, a power analysis was performed to determine the necessary number of patients in each group based on duration of analgesia. With a two-sided type I error of 5% and study power at 80%, it was estimated that 25 patients would be needed in each group in order to detect a difference of 35 min in the duration of analgesia between the two groups.

Continuous variables are expressed as mean ± standard error of the mean or median with the interquartile range as appropriate and categorical variables are reported as percentages. Statistical analysis was done by using Statistica version 6 (StatSoft Inc., Tulsa, Oklahoma, USA; 2001) and GraphPad Prism version 4 (GraphPad Software Inc.; San Diego, California, USA; 2005) software. Continuous variables were normally distributed and were compared by using Student's unpaired *t*-test. Categorical variables were compared by the Chi-square test or Fisher's exact test, as appropriate. All analyses were two-tailed, and *P* < 0.05 was considered statistically significant.

RESULTS

Both groups were comparable with respect to duration of surgery or intravenous sedation for block placement (*P* > 0.05) as shown in Table 1.

Successful block was achieved in 96.7% of patients in both groups and all patients recovered uneventfully without any sensory or motor deficit [Table 2].

The time of onset of the sensory block was statistically significantly shorter in group II while there was no statistically significant difference between both groups regarding the grades of motor block and none of patients experienced a severe (complete) motor block [Table 2].

Mean VAS and the amount of i.v. pethidine needed were statistically significantly lower in group II [Table 2].

No complications were recorded in either groups.

Table 1: Demographic and operative data of the patients receiving bupivacaine or bupivacaine + adenosine for infraclavicular brachial plexus block

	Group I (Bupivacaine) N = 30	Group II (Bupivacaine + Adenosine) N = 30
Age (years)	36.8 ± 9.0	33.5 ± 11.4
Sex (M/F)	16/14	14/16
Weight (kg)	79.1 ± 7.8	82.2 ± 9.5
Height (m)	1.69 ± 0.10	1.67 ± 0.34
Body mass index (kg/m ²)	28.97 ± 2.88	28.38 ± 2.68
Type of operations		
Extensor or flexor tendons repair	1	2
Ulnar nerve transposition	4	3
Trigger finger release	3	2
Excision of hand swelling	5	6
Metacarpal fracture reduction and fixation	9	8
Distal radius pin fixation	5	5
Scaphoid fracture fixation	3	4
Duration of surgery (min)	88 ± 35	90 ± 39
i.v. midazolam (mg)	1.8 ± 0.9	1.9 ± 1.2
i.v. fentanyl (µg)	95 ± 34	90 ± 29

Data are expressed as mean and standard deviation (Mean ± SD)

Table 2: Characters of the infraclavicular block and postoperative pain in patients receiving bupivacaine or bupivacaine + adenosine

	Group I (Bupivacaine) N = 30	Group II (Bupivacaine + Adenosine) N = 30	P value
Success of the block			
Successful block	29 (96.7%)	29 (96.7%)	N/A
Incomplete block	1 (3.3%)	1 (3.3%)	N/A
Failed block	0 (0%)	0 (0%)	N/A
Onset of the sensory block in (min)	20.0 ± 3.1	14.9 ± 2.6	0.01*
Grades of motor block			
Grade IV (Severe = 4)	0 (0%) = 0	0 (0%) = 0	N/A
Grade III (Moderate = 3)	23 (76%) = 69	21 (70%) = 63	0.12
Grade II (Mild = 2)	7 (23%) = 14	9 (30%) = 18	0.10
Grade I (No block = 1)	0 (0%) = 0	0 (0%) = 0	N/A
Score	83	81	0.11
VAS at rest			
30 min postop	2.9 (0-4.5)	2.2 (0-2.9)	0.02*
2 h postop	3.2 (0-4.8)	2.4 (0-3.9)	0.01*
12 h postop	2.2 (0-3.9)	1.2 (0-2.2)	0.01*
24 h postop	3.1 (0.5-4.8)	1.6 (0-3.0)	0.004*
36 h postop	3.3 (1-5.3)	1.7 (0-3.0)	0.004*
48 h postop	1.4 (0-2.5)	1.0 (0-1.9)	0.06
Time to first rescue analgesia (min)	255 ± 126	299 ± 135	0.002*
IV pethidine (mg) needed over 48 h	56.6 ± 33.4	25.5 ± 25.1	0.002*
No. of patients needed i.v. pethidine	30 (100%)	25 (83%)	0.01*

Data are expressed as mean and standard deviation (Mean ± SD) or median with interquartile range. *Denotes statistical significance ($P < 0.05$) N/A: Nonapplicable; VAS: Visual analog score

DISCUSSION

The results of this study showed an analgesic effect of infraclavicular adenosine as evidenced by shorter time of onset of the sensory block, lower VAS, and lower opioid requirements.

Many studies in humans have shown pain-reducing effects of i.v. adenosine.^[11,12]

These results stated that adenosine has both central and peripheral analgesic effects. This may be through both central A1-receptor-mediated antinociception, and

inhibition of peripheral inflammatory processes via A2A and A3 receptors.

Intrathecal injection of adenosine analogues have been used in the management of chronic neuropathic and inflammatory pain.^[13,14] However, there are few studies that used adenosine in peripheral nerve blocks.

Gan *et al.*^[15] reported that i.v. adenosine perioperatively improves postoperative recovery, as indicated by lower pain scores and less opioid consumption.

Apan *et al.*^[16] studied the effect of perioperative intravenous adenosine infusion on the brachial plexus block performed via an axillary approach with lidocaine 1.25% and epinephrine 1/200,000. Adenosine $80 \mu\text{g kg}^{-1} \text{min}^{-1}$ or saline (control) was infused intravenously in a double-blind manner for 1 h. The time to pain feeling was significantly longer in the adenosine group compared to the control group (438 ± 387 vs. 290 ± 227 min, $P = 0.02$). Whereas, the pain scores, time to first rescue analgesic, and total analgesic requirements showed no difference.

The effects of subarachnoid administration of adenosine analogs on substance P concentrations in cerebrospinal fluid were investigated in rats.^[13] The authors reported that subarachnoid injection of adenosine analogs reduces the substance P in cerebrospinal fluid and produces behavioral effects that denote antinociception in rats.

In another study^[14] on a rat model of neuropathic pain, the effect, mechanisms of action, and interaction with noradrenergic systems of subarachnoid adenosine was studied. The authors concluded that, after nerve injury, adenosine reduces hypersensitivity through spinal norepinephrine release and recommended its use in the treatment of chronic pain states.

In contradiction with our findings, some studies reported that adenosine has no analgesic effect. Habib *et al.*^[17] reported that i.v. adenosine had no analgesic effect in major gynecologic surgery. The patients were randomly allocated to receive four different doses of adenosine (25, 50, 100, or $200 \mu\text{g kg}^{-1} \text{min}^{-1}$) or matching placebo. Opioid use during the initial 24-h period after surgery was not significantly different between groups. The groups showed no differences regarding the cumulative anesthetic use, pain scores, patient satisfaction with pain control, intraoperative opioid requirements, sedation, opioid-related symptom distress scores, time to readiness for discharge from the postanesthesia care unit, time to readiness for discharge from the hospital, and occurrence of adverse events.

In addition, Rane *et al.*^[18] stated that intrathecal adenosine had no analgesic effect in 25 healthy parturients requesting labor analgesia. Patients received $10 \mu\text{g}$ of sufentanil + $500 \mu\text{g}$ of adenosine or $10 \mu\text{g}$ of sufentanil intrathecally. Pain scores showed no difference between groups. Analgesia duration has not significantly increased by adenosine + sufentanil, 99 ± 54 min, vs. sufentanil, 89 ± 56 min. Apan *et al.*^[19] studied the effect of adding adenosine to prilocaine and lignocaine for brachial plexus block. The block was done using a 35-ml mixture 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. Both groups showed no significant differences with respect to onset of sensory and motor block. Time to first pain sensation after the block was not significantly longer in the adenosine group 379 ± 336 min vs. the control group 304 ± 249 min ($P = 0.14$). Furthermore, both groups showed no significant differences with respect to time to first analgesic requirements and postoperative 24h analgesic consumption.

These contradictory results reported in the Rane and Apan studies can be explained by the fact that adenosine (with a short half life as it requires a continuous infusion mostly at $80\text{--}150 \mu\text{g kg}^{-1} \text{min}^{-1}$) would have no effects when given as a single dose.

It should be addressed that we can not fully exclude that the analgesic effect of adenosine resulted from a pharmacokinetic effect of mixing adenosine with bupivacaine and this fact may impose a limitation to this study.

Another limitation to our study is the prolonged local anesthetic administration that might increase the duration of motor block which is a major disadvantage during these minor surgical procedures which can be managed as outpatient cases.

CONCLUSION

Based on the findings of our study, infraclavicular adenosine had analgesic effects and may provide valuable addition to the therapeutic options in anesthesia and pain management. Further research is required to figure out the exact role of adenosine.

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