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Effects of intravenous adenosine 5′-triphosphate on intraoperative hemodynamics and postoperative pain in patients undergoing major orofacial surgery: a double-blind placebo-controlled study

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Abstract
Purpose. We conducted a double-blind placebo-controlled study to investigate the effects of the intraoperative intravenous infusion of adenosine 5′-triphosphate (ATP) on intraoperative hemodynamics and postoperative pain in patients undergoing major orofacial surgery.
Methods. Thirty patients (age, 16–42 years; 16 males/14 females) scheduled for sagittal split ramus osteotomy were assigned in a double-blind fashion to receive intraoperative intravenous infusion of ATP ($n = 15$) or saline ($n = 15$). Anesthesia was induced and maintained with propofol, fentanyl, and vecuronium. Local anesthesia was added for intraoperative analgesia. In the ATP group, ATP was infused at a rate of 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ throughout surgery. Postoperative pain was managed with intravenous patient-controlled analgesia (PCA) with morphine. The intensity of postoperative pain was assessed with a verbal numeric rating scale (NRS). Morphine consumption was also assessed.
Results. There were no differences in demographic, anesthetic, and surgical data between the ATP and placebo groups. Intraoperatively, ATP effectively suppressed responses of blood pressure and heart rate to painful surgical stimuli. There were no differences in postoperative NRS scores between the two groups. However, postoperative morphine consumption was significantly less in the ATP group, compared with the placebo group, throughout the 72-h postoperative observation period. Cumulative morphine consumption for 72 h postoperatively was 47% less with ATP, compared with placebo. No adverse effect of ATP was observed.
Conclusion. Our data suggest that intraoperative ATP infusion can blunt hemodynamic responses to surgical stimuli and produce prolonged analgesia in patients undergoing major orofacial surgery.

Key words Postoperative pain · Analgesia · Adenosine triphosphate · Orofacial surgery · Hemodynamics

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Introduction

In a variety of animal pain models, intrathecal injection of adenosine or its analogue reduces pain behavior primarily via A1 purinoceptor activation [1]. Clinically, several studies have shown that intravenous infusion of adenosine during surgery reduces postoperative pain [2–6]. In contrast to adenosine, intrathecal as well as local injection of adenosine 5'-triphosphate (ATP) evokes severe pain and allodynia in animals via P2X purinoceptor activation [7–9]. However, intravenous ATP may reduce postoperative pain, analogous to adenosine, because ATP is converted to adenosine within seconds via the action of ectonucleotidases in the bloodstream [10,11]. Actually, we have recently found that intravenous infusion of ATP can alleviate neuropathic pain [12,13], analogous to adenosine [14,15]. To date, however, the effects of intravenous ATP on pain control during and/or after surgery have not been investigated in humans.

The aim of the present study was to investigate, in a double-blind placebo-controlled manner, the effects of intravenous ATP on intraoperative hemodynamics, as well as postoperative pain, in patients undergoing sagittal split ramus osteotomy (a painful procedure including bone dissection).

Patients and methods

After obtaining approval from the institutional clinical research ethics committee and written informed consent from patients, and parents if required, we enrolled in the study 30 American Society of Anesthesiologists (ASA) I patients (age, 16–42 years; 16 males and 14 females) scheduled to undergo sagittal split ramus osteotomy for mandibular prognathism. Patients with known pregnancy, asthma, gout, or heart block, or those taking

methylxanthine medications were excluded. Patients were instructed not to take caffeine-containing beverages for at least 24 h before surgery. Patients were randomly allocated to an ATP group (15 patients, 8 males) and a placebo group (15 patients, 8 males), according to a randomization list prepared for males and females separately. On the day of surgery, the medication (ATP or placebo) was supplied in identical 50-ml syringes labeled with the randomization number and the drug name "ATP/placebo for Clinical Trial". The data code was broken after the completion of the study.

Patients were premedicated with oral diazepam (10 mg) and famotidine (150 mg) at 90 min before induction of anesthesia. General anesthesia was induced with a bolus intravenous injection of fentanyl (5 $\mu g \cdot kg^{-1}$) and target-controlled infusion (TCI) of propofol at a target blood concentration of 3.5 $\mu g \cdot ml^{-1}$, using a TCI pump (TE-371; Terumo, Tokyo, Japan). Immediately after patients lost consciousness and eyelash reflex, intravenous infusion of ATP (Adetphos-L3 [1% solution]; Kowa, Nagoya, Japan) at a constant rate of 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or infusion of normal saline at the equivalent infusion rate (0.96 $ml \cdot kg^{-1} \cdot h^{-1}$) was initiated, using a syringe infusion pump (TE-331; Terumo). The dose of 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was employed based on our preliminary dose-response study showing that this was the maximum nonhypotensive dose of ATP in anesthetized patients (data not shown). Vecuronium (0.1 $mg \cdot kg^{-1}$) was given to facilitate nasotracheal intubation. Intraoperatively, general anesthesia was maintained with propofol at a target blood concentration of 3–6 $\mu g \cdot ml^{-1}$ and vecuronium at 0.08 $mg \cdot kg^{-1} \cdot h^{-1}$. Lungs were ventilated with oxygen-enriched air (fraction of inspired oxygen [$F_{I_{O_2}}$], 0.4). Five min prior to the start of surgery, right inferior alveolar nerve block was performed with 4 ml of 2% lidocaine containing epinephrine (12.5 $\mu g \cdot ml^{-1}$) near the mandibular foramen, and local infiltration anesthesia was performed on the right side of the operative field with 4 ml of the same anesthetic. First, sagittal transection of the right mandibular branch was conducted. Then, the sagittal transection of the left mandibular branch was conducted after performing alveolar nerve block and local infiltration anesthesia on the left side. Finally, the bilateral mandibular bone segments were fixed in appropriate positions, and intermaxillary fixation was placed.

Invasive radial arterial pressure, five-lead electrocardiogram, heart rate, end-tidal carbon dioxide tension, and arterial oxygen saturation by pulse oximetry were monitored. Arterial blood gas was analyzed every 20 min. At the end of surgery, infusion of ATP or saline was terminated, and the neuromuscular blockade was antagonized. The trachea was extubated after the recovery of adequate levels of consciousness and spontaneous breathing.

Systolic blood pressure (SBP) and heart rate (HR) were recorded at the following eight time points: (1) immediately before induction of anesthesia (preinduction); (2) after induction of anesthesia, immediately prior to tracheal intubation (postinduction); (3) at 5 min after tracheal intubation (postintubation); (4) immediately before the start of surgery (preoperation); (5) during the right mandibular branch transection (early operation); (6) during the left mandibular branch transection (late operation); (7) immediately after the end of surgery (postoperation); and (8) at 10 min after tracheal extubation (postanesthesia). Anesthesiologists were instructed to maintain intraoperative SBP within ±20% of the "preoperation" value solely by adjusting the target blood concentration of propofol. The use of ephedrine, nicardipine, atropine, and propranolol was allowed for the treatment of hypotension (SBP < 80 mmHg), hypertension (SBP > 140 mmHg), bradycardia (HR < 40 bpm), and tachycardia (HR > 110 bpm), respectively.

Fifteen min after tracheal extubation, patients were asked if analgesics were necessary. If necessary, morphine was given intravenously en bolus in increments of 1 mg every 2.5 min until patients were satisfied. Then, intravenous patient-controlled analgesia (PCA) with morphine was commenced using a CADD-Legacy PCA pump (Smiths Medical Japan, Tokyo, Japan). Bolus dose on demand and lockout time were set at 1 mg and 10 min, respectively. Continuous background infusion was not employed. PCA was continued for 72 h postoperatively. Intravenous morphine, 2 mg, could be added as a rescue dose whenever analgesia was unsatisfactory. When treatment-refractory side effects of morphine occurred, PCA was discontinued and rectal diclofenac sodium (50 mg) was used as an alternative analgesic.

The morphine dose required for initial titration was recorded. Then, the PCA morphine dose was recorded at 24, 48, and 72 h postoperatively. The intensity of pain at rest and the level of sedation were rated by an 11-point verbal numeric rating scale (NRS), with 0 indicating no pain and 10 the worst pain imaginable, and a Ramsay sedation (RS) score [16], respectively, at 2, 24, 48, and 72 h postoperatively. All episodes of nausea, vomiting, and high fever (38.5°C or more) were recorded. Severe nausea and/or vomiting were treated with droperidol (up to 5 mg). High fever was treated with rectal diclofenac sodium (50 mg). Venous blood was sampled at 24 h postoperatively for measurements of the white blood cell (WBC) count and serum C-reactive protein (CRP).

A-priori power analysis indicated that a sample size of 15 patients in each group would be adequate to detect a 30% reduction in the postoperative morphine consumption with a power of 0.8 (alpha = 0.05). All parametric data were compared between groups using the

unpaired *t*-test. Repeated-measures analysis of variance (ANOVA) was used to examine changes in SBP and HR. When a significant difference was noted, the Bonferroni-Dunn test was performed for multiple comparisons within groups. Nonparametric variables and frequency variables were compared between groups using the Mann-Whitney *U*-test and χ^2 test, respectively. $P < 0.0018$ was considered significant for multiple comparisons of SBP and HR within a group by the Bonferroni-Dunn test. Otherwise, $P < 0.05$ was considered statistically significant. Data are expressed as means ± SD or medians (percentiles and/or ranges).

Results

Three patients in the placebo group dropped out of the study because PCA morphine was discontinued due to treatment-refractory nausea. Therefore, data from 12 and 15 patients in the placebo and ATP groups, respectively, were analyzed. There were no statistically significant differences between the groups in age, sex, body weight, operation time, anesthesia time, or the dose of propofol (Table 1).

Alterations in hemodynamics requiring pharmacological treatment were not observed in any patients in either group. In both groups, SBP decreased significantly in the "postinduction", "postintubation", and "preoperation" phases, compared with the "preinduction" phase (Fig. 1). SBP increased significantly in "early operation" and "late operation" phases, compared with the "preoperation" phase, in the placebo group, but not in the ATP group (Fig. 1). There were no intergroup differences in SBP in the "preinduction", "postinduction", "postintubation", or "preoperation" phases, whereas SBP was significantly higher in the placebo group than in the ATP group in the "early operation" and "late operation" phases (Fig. 1). In both groups, HR increased significantly in the "preoperation" phase, compared with the "postintubation" phase (Fig. 1). HR increased significantly in the "early operation" phase, compared with the "preoperation" phase, in the placebo group, but not in the ATP group (Fig. 1). HR was higher in the ATP group than in the placebo group in the

Table 1. Demographic, surgical, and anesthetic data of the placebo and ATP groups

	Placebo group ($n = 12$)	ATP group ($n = 15$)
Age (years)	26 ± 6	22 ± 6
Weight (kg)	63 ± 9	59 ± 12
Sex (male/female)	7/5	8/7
Duration of surgery (min)	125 ± 27	109 ± 17
Duration of anesthesia (min)	186 ± 21	174 ± 16
Average propofol infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)	11.1 ± 0.7	11.3 ± 1.7
Total propofol dose (mg)	2137 ± 293	1913 ± 382
Total ATP dose (mg)	—	1476 ± 383
ATP infusion time (min)	—	149 ± 13

Data are shown as means ± SD
There were no significant intergroup differences in any of the data shown

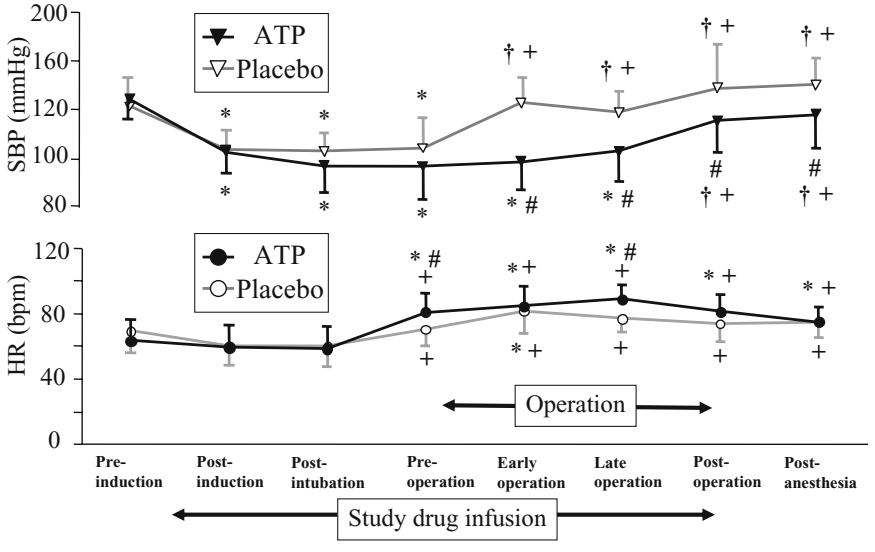

Fig. 1. Changes in systolic blood pressure (*SBP*) and heart rate (*HR*) during anesthesia in adenosine 5′-triphosphate (*ATP*) and placebo groups. Data are expressed as means ± SD. $^{*}P < 0.0018$ vs pre-induction; $^{+}P < 0.0018$ vs post-intubation; $^{\dagger}P < 0.0018$ vs pre-operation by Bonferroni-Dunn test, and $^{\#}P < 0.05$ vs placebo by unpaired *t*-test

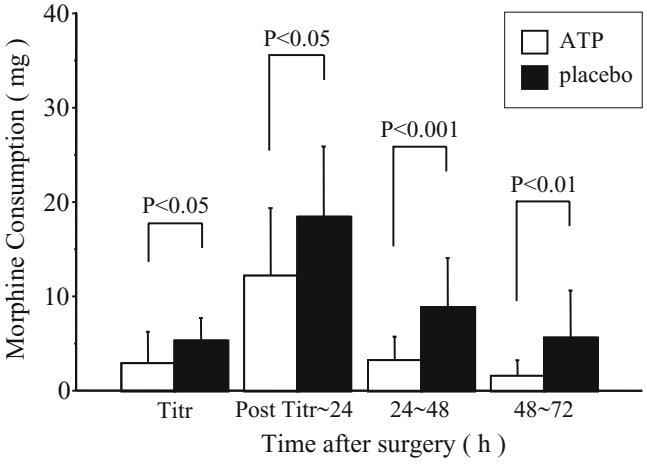

Fig. 2. Morphine consumption in the ATP group (*open bars*) and the placebo group (*closed bars*) in each designated period. Initially, i.v. bolus morphine was titrated to satisfactory analgesia. Then patient-controlled analgesia (PCA) with intravenous morphine was commenced and continued for 72 h postoperatively. Values for postoperative morphine consumption delivered by initial titration (*Titr*) and by PCA during the first (*post Titr~24*), second (*24~48*), and third (*48~72*) postoperative 24-h periods are shown as means ± SD. Data were compared between groups with the unpaired *t*-test

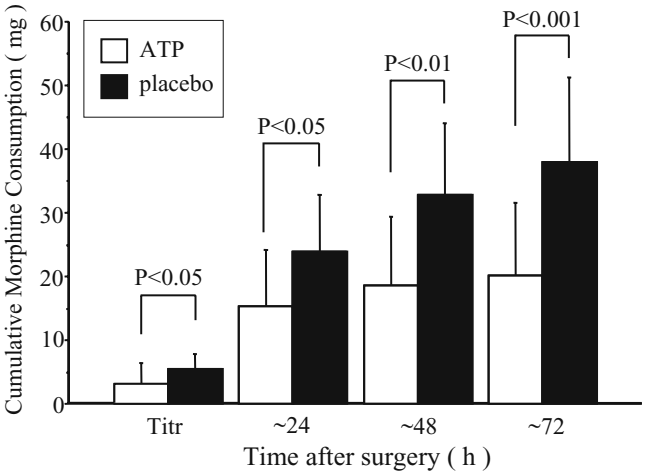

Fig. 3. Cumulative morphine consumption in the ATP group (*open bars*) and the placebo group (*solid bars*) at each designated time. Initially, intravenous bolus morphine was titrated to satisfactory analgesia. Then patient-controlled analgesia (PCA) with intravenous morphine was commenced and continued for 72 h postoperatively. Values for cumulative morphine consumption at initial titration, and at 24, 48, and 72 h postoperatively are shown as means ± SD. Data were compared between groups with the unpaired *t*-test

"preoperation" and "late operation" phases (Fig. 1). There was no abnormal finding for intraoperative blood gas in either group. No adverse effect of ATP was noted perioperatively.

The morphine dose required for the initial titration was significantly less, by 45%, in the ATP group, compared with the placebo group (Fig. 2). The number of patients requiring the initial morphine titration was significantly lower in the ATP group than in the control group (10 out of 15 vs 12 out of 12; $P < 0.05$). PCA morphine doses required during the first, second, and third postoperative 24-h periods were significantly less, by 34%, 63%, and 73%, respectively, in the ATP group, compared with the placebo group (Fig. 2). Cumulative morphine consumption was also less in the ATP group, compared with the control group, by 36%, 43%, and 47% at 24 h, 48 h, and 72 h after surgery, respectively (Fig. 3). During the PCA period, no patient in either group required a rescue morphine dose.

NRS scores remained at relatively low levels (1–5) in all the patients in both groups throughout the 72-h observation period. There were no significant intergroup differences in time from the end of surgery to tracheal extubation, NRS scores (Fig. 4), or RS scores (Table 2). There was no intergroup difference in the number of patients experiencing postoperative nausea and/or vomiting, even when excluded data were reincluded for data analysis (Table 2). There were no significant intergroup differences in the WBC count, CRP level, or numbers of patients with high fever requiring rectal diclofenac sodium, though the CRP level at 24 h postoperatively tended to be less ($P = 0.074$) and the number of patients with high fever tended to be lower ($P = 0.076$) in the ATP group, compared with the placebo group (Table 2).

Discussion

In the present study, intravenous infusion of ATP significantly suppressed intraoperative hemodynamic responses to noxious surgical stimuli and significantly reduced postoperative morphine consumption at a similar degree of pain relief, compared with placebo, without producing noticeable adverse effects in patients undergoing sagittal split ramus osteotomy. The morphine-sparing effect of ATP lasted as long as 72 h postoperatively, and ATP decreased cumulative 72-h morphine consumption by 47%. These results suggested that intravenous infusion of ATP could blunt hemodynamic responses to noxious surgical stimuli and provide prolonged and profound perioperative analgesia to patients undergoing painful orofacial surgery. We used ATP in the present study mainly because an intravenous formulation of ATP, but not adenosine, was commercially available in Japan at the time of the study, and because we assumed that ATP could be used as a substitute for adenosine, though an intravenous

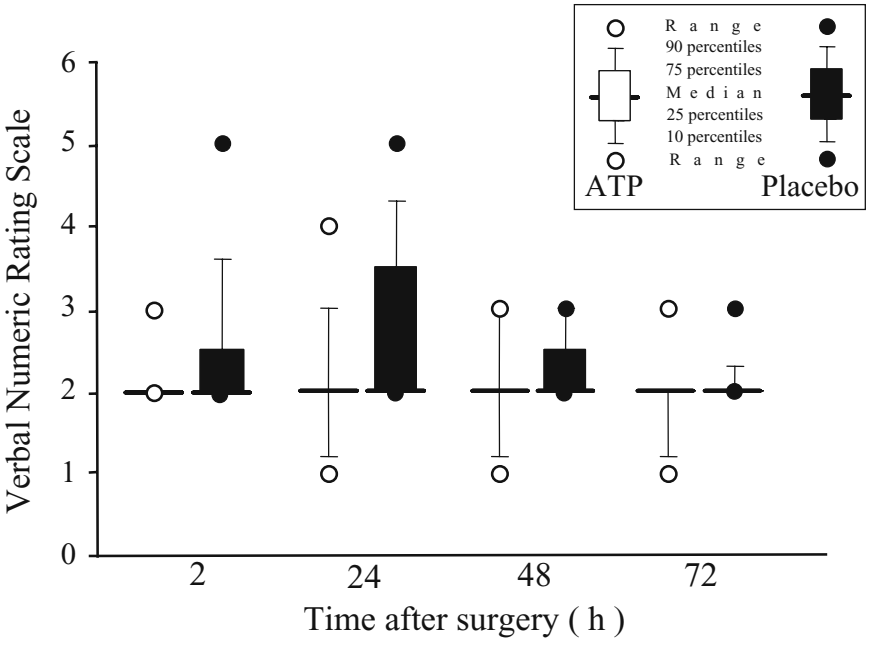

Fig. 4. Verbal numeric rating scale (NRS) scores in the ATP group (*open bars and circles*) and the placebo group (*closed bars and circles*) at each designated time. Data are shown as medians, percentiles, and ranges. There were no differences in NRS scores between the ATP and placebo groups

Table 2. Time from the end of surgery to extubation; postoperative sedation scores; frequency of nausea and vomiting; WBC count; CRP; and frequency of high fever in the placebo and ATP groups

	Placebo group (n = 12)	ATP group (n = 15)
Time to extubation (min)	9.5 ± 6.4	7.1 ± 3.4
Sedation score		
2 h	3 (2–3)	2 (2–3)
4 h	3 (2–3)	2 (2–3)
24 h	3 (2–3)	2 (2–3)
48 h	3 (2–3)	2 (2–3)
72 h	3 (2)	2 (2)
Patients with nausea[a]	4/12 (7/15)	4/15
Patients with vomiting[a]	0/12 (0/15)	0/15
WBC ($\cdot ul^{-1}$) (24 h)	12 138 ± 2789	10 794 ± 2442
CRP ($mg \cdot dl^{-1}$) (24 h)[b]	6.48 ± 2.78	4.80 ± 2.11
Patients with high fever[b]	4/12	1/15

Data are shown as means ± SD, medians (ranges), or frequencies
[a]There was no significant difference between groups even when excluded data were re-included for data analysis, as shown in parentheses
[b]Although there was no significant intergroup difference in these data, the CRP level at 24 h postoperatively tended to be less (P = 0.074) and the number of patients who required diclofenac sodium for treatment of high fever tended to be less (P = 0.076) in the ATP group, compared with the placebo group

formulation of adenosine is currently available for a strictly limited clinical indication of diagnostic cardiac scintigraphy.

It has been reported that intravenous infusion of adenosine at doses of up to 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ does not decrease blood pressure (BP) or heart rate (HR) in conscious humans [17]. The maximum nonhypotensive dose of ATP in anesthetized patients was found to be 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in our preliminary study. Therefore, this dose was employed in the present double-blind study so that anesthesiologists could not distinguish between ATP and placebo from a differing hemodynamic response to the drugs. Actually, ATP at 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ did not significantly decrease SBP, compared with placebo, until the start of surgery. In both groups, HR increased significantly in the "preoperative" phase, compared with the "postintubation" phase, presumably due to the β-adrenoceptor-stimulating effect of epinephrine contained in the local analgesic solution given preoperatively. Reflex tachycardia in

response to the vasodilating effect of adenosine compounds [18] may also have contributed to the increase in HR in the ATP group, because the preoperative increase in HR was slightly greater in the ATP group, compared with the placebo group. After the beginning of surgery, SBP increased significantly in response to noxious surgical stimuli in the placebo group, but not in the ATP group. Likewise, HR increased significantly in response to noxious surgical stimuli in the placebo group, but not in the ATP group. The ATP-induced suppression of hemodynamic responses to surgery suggested that the adenosine compound blunted the hemodynamic responses to noxious surgical stimuli through its antinociceptive rather than vasodilating effect.

Postoperatively, ATP produced a significant morphine-sparing effect that lasted as long as 72 h. This suggested that ATP produced prolonged postoperative analgesia. Although the precise mechanisms underlying the ATP-induced prolonged analgesia are unclear, it has been reported that intravenous infusion of adenosine can blunt hemodynamic responses to surgical stimuli [2–6], reduce intraoperative anesthetic requirements [2–4], replace intraoperative opioids [5,6], reduce postoperative opioid requirements for analgesia [2,4–6], and/or reduce the intensity of postoperative pain [5,6]. It has been shown that adenosine produces antinociception primarily via the activation of A_1 purinoceptors in the spinal dorsal horn [1, 18]. Given that A_1 receptors exist not only on dorsal root ganglion neurons and spinal dorsal horn neurons but also in the trigeminal ganglia and possibly in the trigeminal nucleus [19,20], it is conceivable that adenosine can inhibit trigeminal nociceptive transmission [20], thereby reducing orofacial pain. When administered intravenously, ATP is converted to adenosine within seconds in the circulating blood [10,11] and thus may reach effectors as adenosine. Therefore, it is likely that the prolonged and profound perioperative analgesia produced by intravenous ATP in patients undergoing major orofacial surgery resulted from the extended antinociceptive effect of adenosine that can by far outlast the infusion period [21].

It is possible that the stable hemodynamics as well as the postoperative pain relief seen in the present study may not be due to adenosine derived from ATP but may be due to ATP itself, because we did not measure blood levels of adenosine in this study. Several lines of evidence, however, support our assumption that ATP which was converted to adenosine extremely rapidly after exogenous administration acted on effectors as adenosine. First, although the most prominent direct actions of adenosine and ATP on the heart are depression of atrioventricular (AV) nodal conduction via A1 purinoceptors [22] and a positive inotropic effect via P2X purinoceptors [23], respectively, both adenosine and ATP given in rapid intravenous bolus uniformly depress AV nodal conduction and thus can convert almost all episodes of paroxysmal supraventricular tachycardia involving the AV node [22]. Second, although the direct actions of adenosine and ATP on the vascular smooth muscle are vasodilation via A2A purinoceptors and vasoconstriction via P2X purinoceptors, respectively [24,25], both intravenous adenosine and ATP equally cause dose-dependent vasodilation and hypotension [26]. Third, although the direct actions of adenosine and ATP on the spinal cord are antinociception via A1 purinoceptors [1] and pronociception via P2X purinoceptors [7,8], respectively, both intravenous adenosine and ATP analogously relieve neuropathic pain [12–15]. Fourth, although adenosine and ATP are known to act as anti-inflammatory and pro-inflammatory substances, respectively [25], our present data suggest an anti-inflammatory rather than pro-inflammatory property of intravenous ATP, as described below. Last, although nucleosides such as adenosine and uridine can cross the blood-brain barrier (BBB) by means of nucleoside transporter systems located in the BBB and then can be converted to nucleotides such as ATP and uridine 5′-triphosphate (UTP) in the cerebral tissues, nucleotides per se cannot be transported across the BBB [21,27–29]. It is thus likely that intravenous ATP acted as adenosine on effectors in the central nervous system, mainly because ATP, unlike adenosine, cannot cross the BBB.

Segerdahl et al. [2–4] conducted studies to assess the effects of intraoperative adenosine infusion in patients undergoing breast surgery, shoulder surgery, and abdominal hysterectomy. Intraoperative infusion of adenosine at a relatively low dose ($80\ \mu g \cdot kg^{-1} \cdot min^{-1}$) reduced inhalational anesthetic requirements by 20%–50% and kept intraoperative SBP levels more stable and less responsive to painful surgical stimuli, compared with placebo [2–4]. After breast surgery and abdominal hysterectomy, postoperative opioid requirements during the first 24 h were reduced by 27% and 18%, respectively, at a similar degree of pain relief, suggesting an extended analgesic effect of adenosine [2, 4]. Zarate et al. [5] compared the effects of adenosine at relatively high doses ($166 \pm 17\ \mu g \cdot kg^{-1} \cdot min^{-1}$), given intraoperatively as an adjunct to inhalational anesthesia, with those of remifentanil in patients undergoing gynecological surgery. They found that adenosine and remifentanil were equally effective in inhibiting cardiovascular responses to painful surgical stimuli and that treatment with adenosine resulted in greater pain relief, lasting as long as 12 h, and a reduction in 24-h morphine consumption by 28%, compared with treatment with remifentanil [6]. Fukunaga et al. [6] conducted a similar comparative study using adenosine at higher doses ($292 \pm 82\ \mu g \cdot kg^{-1} \cdot min^{-1}$) in patients undergoing gyneco-

logical or orthopedic surgery. They found that treatment with adenosine resulted in 50% and 42% reductions in 24-h and 48-h morphine consumption, respectively, together with greater pain relief, lasting as long as 48 h, compared with treatment with remifentanil [6]. ATP at 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ employed in the present study was equivalent to adenosine at 105 $\mu g \cdot kg^{-1} \cdot min^{-1}$, given the 1.5 times greater molecular weight of ATP than adenosine [15]. With this dose, we observed 36% to 47% reductions in morphine consumption, lasting as long as 72 h, at a similar degree of pain relief, again confirming the extended perioperative analgesic effects of adenosine compounds. by far outlasting the infusion period. Comparisons of data from previous studies [2–6] with data from the present study, in terms of drug doses, reductions in morphine consumption, and reductions in pain scores suggest that the perioperative analgesic effects of adenosine compounds are grossly dose-dependent.

Clearly, inflammatory reactions following tissue injury contribute significantly to postoperative pain. It has been suggested that adenosine produces anti-inflammatory effects in tissues via the activation of peripherally located A_{2A} or A_3 purinoceptors [18, 25, 30, 31]. Therefore, peripheral A_{2A} or A_3 purinoceptor-mediated anti-inflammatory action, in addition to central A_1 purinoceptor-mediated antinociceptive action, probably contributed to the prolonged analgesia induced by intravenous ATP. In the present study, the CRP level at 24 h postoperatively and the number of patients who required diclofenac sodium for the treatment of high fever tended to be lower in the ATP group, compared with the placebo group. These findings may reflect the anti-inflammatory effect mediated by the A_{2A} or A_3 purinoceptors.

In conclusion, intravenous infusion of ATP at 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ given during sagittal split ramus osteotomy significantly blunted the hemodynamic responses to noxious surgical stimuli, and significantly reduced postoperative 72-h morphine consumption, by 47%, without causing noticeable adverse effects. The morphine-sparing effect of ATP lasted as long as 72 h postoperatively, suggesting a prolonged and profound analgesic effect of intravenous ATP, by far outlasting its infusion period. Intraoperative infusion of ATP seems to be a useful pharmacological tool for stabilizing intraoperative hemodynamics and achieving prolonged and profound perioperative analgesia in patients undergoing painful orofacial surgery.

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