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Intravenous Acetaminophen, A New Option for Postoperative and Pediatric Pain Management: Literature Review

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ABSTRACT

Background: As a result of the side effects of opiates, intravenous acetaminophen has been recently introduced for pain management, an issue that was previously controversial in clinical practice. We aim to explore its efficacy in acute pain control, pediatric and regional anesthesia.

Methods: We searched the studies and literatures in the PubMed mainly focusing on the recent 5 years about IV acetaminophen.

Results: Some studies presented its advantages, while others declined it.

Conclusion: Correct practice of intravenous acetaminophen is clinically safe demonstrating some advantages by its use alone. However, as one part of multimodal analgesia, it needs more evidences to prove its efficacy as compared with PO formula and other pain-release agents.

KEYWORDS

Acetaminophen; Postoperative Pain; Paediatric Pain.

INTRODUCTION

Background

Acetaminophen as an analgesic and antipyretic agent treated for headache and fever has been marketed in the US in 1953 [1]. Intravenous Acetaminophen (IVA), as a new formulation, has been approved to use in approximately 80 countries in Europe, Asia-Pacific, Middle East, Africa, and other regions outside the United States [2]. However, in USA, It is just approved by FDA in 2010. Majority of studies demonstrated its' effectiveness in acute pain perioperatively including gynecologic surgery, orthopedic surgery, bariatric surgery, and others [3-11]. The use of IVA in the pediatric population is also starting to gain popularity with investigators evaluating its cost and efficacy in children undergoing surgery. The anti-inflammatory properties of IVA and their potential role in cardiac surgery have also been reviewed as well as its use in intravenous regional anesthesia. We aim to review the current literature on IVA and its use in the perioperative and pediatric pain management.

Perioperative pain and narcotic consumption

Management of pain during the perioperative period can include preemptive, preventive, and/or rescue (postoperative) analgesia. Opiates, such as oxycodone, morphine, hydromorphone, fentanyl, and sufentanyl, have always been used clinically to control acute pain postoperatively because of their effectiveness. Meanwhile, opiates presented its' adverse effects including postoperative nausea and vomiting (PONV), pruritus and constipation, ileus, bladder dysfunction, and respiratory depression [12-14]. On account of these side effects, patients increased the risk and prolonged the duration of hospital stay. In 2004, the American Society of Anesthesiologists Task Force on Acute Pain Management recommended a multimodal analgesic approach for the management of acute pain in order to reduce opioid-induced adverse effects. The practice guidelines for acute pain management in the perioperative setting specifically state "unless contraindicated, all patients should receive around-the-clock regimen of no steroidal anti-inflammatory

drugs (NSAIDs), selective cyclooxygenase-2 Inhibitors (COXIBs), or acetaminophen [15]. Ketorolac is a powerful nonsteroidal anti-inflammatory medication (NSAIDs) which is used in clinic prevalently. The mechanism of ketorolac is to inhibit COX1 and COX2, which combined complications including GI bleeding, GI mucosal damage, renal impairment, postoperative bleeding due to COX1 inhibition 2 [16]. COXIBs is a high selective COX2 inhibitor which is used in clinic for acute pain recently. COXIBs inhibited COX2 in blood vessel decreasing production of prostacyclin. Prostacyclin prevents platelet aggregation and vasoconstriction. Therefore, the inhibition can lead to excess clot formation and higher blood pressure, which increased cardiovascular accident [17]. Ketamine is often reserved for chronic pain patients in the perioperative period, and having hallucinations as a potential side effect as well as the risk for tachycardia and hypertension, limit its use [18, 19]. Compared with NSAIDs, IVA has no anti-inflammatory effect exerting its effects mainly through inhibition of COX2 pathway in synthesis of prostaglandin (PGE) which has been found as a mediator of nociception. [20-23]. Thus, IVA is rarely associated with bleeding secondary to platelets dysfunction as previously stated in various reports. The most serious side effects of overdose acetaminophen were hepatotoxicity. Recently, one case has been reported that a 36-years-famale received acetaminophen every 6 hours totally 16 doses both preoperatively and postoperatively for pain control. Then her aspartate aminotransferase and alanine aminotransferase levels were elevated and peaked at 4,833 and 6,600 IU/L, respectively [24]. A retrospective study evaluated 300 patients receiving IVA from August 2011 till August 2012. No case reports of any liver dysfunction based on FDA-proved dose even in 10 patients (3%) who had a documented history of liver disease [25].

We collected some retrospective studies focusing on narcotic consumption with administration of IVA. A retrospective cohort study by Gonzalez et al. compared opioid consumption in 24 hours postoperatively after bariatric surgery in patients who received IVA or not. (99.5mg vs. 164.6mg, P = 0.018). There was nearly 40% reduction as compared to patients not given IVA [3]. This finding was similar with another retrospective study by Saurabh et al. who identified 183 patients that received scheduled IV acetaminophen in addition to morphine sulfate (MSO4) patient-controlled analgesia (PCA) after laparoscopic Rou-en-Y surgery. The opioid consumption was significantly different between non-IVA group and IVA group (average of 29.9 versus 24.1 mg of MSO4; P < 0.05) [4]. A recent meta-analysis further supports the findings of these studies. The meta-analysis included 11 randomized, controlled trials consisting of 740 patients that received a single dose of IVA either pre- or intra-operatively. The analysis included several types of surgery - hysterectomy, thyroidectomy, hand surgery, tonsillectomy, gynecological procedures, and laparoscopic cholecystectomy. The study showed lower pain scores, decreased total opioid consumption, and decreased nausea vomiting in patients that received IVA [5]. In contrast, other retrospective studies demonstrated IVA didn't decrease narcotic consumptions. Raiff et al. reviewed randomly 176 patients who underwent total knee or hip replacement surgery from Duke University Hospital (DUH). 88 patients received single-dose IVA. There was no significant difference in 24 hours oral morphine consumption (149.3mg vs. 147.2mg, P = 0.904). The average length of PACU was also not statistically significant (163min vs. 169, P = 0.588) [6]. This retrospective cohort study didn't present what type of anesthesia the patients underwent (GA, SA, CEA or CSEA). As well, they listed patients given Ropivacaine or Bupivacaine but didn't show if this was nerve block, intra-articular and so on. An analogous retrospective study by Kelly et al. enrolled 100 patients (25 for IVA group and 75 for non-IVA group) and found there was no significant difference between two groups in total morphine consumption (135mg vs. 112.5mg, P = 0.987) and daily morphine consumption (45mg/day vs. 37.5mg/day, P = 0.845). The median hospital length of stay was 3 days in both groups (P = 0.799) [7]. They also didn't indicate the type of anesthesia, any block combined as above. A retrospective cohort study of patients undergoing gynecologic procedures was conducted to assess the impact of adding scheduled IV acetaminophen to postoperative analgesic regimens from 2009-2013. 137 patients were enrolled in this study. There was no difference in opioid requirements between the groups (21 mg [interquartile range, IQR, 15-39.8 mg] vs. 32.6 mg [IQR, 16.75-41 mg], P = 0.150). The average pain score and incidence of adverse effect were no different between two groups [8]. However, at first, they didn't point out which kind of gynecologic surgery was enrolled. Different surgery has different trauma and different class of pain. Secondly, the control group included patients from 2009 to 2011 (before IVA was on formulary) and IVA patients were 2011 to 2013. Thirdly, they didn't indicate if patients had GA vs. MAC, intra operative dose of opiates and whether or not patients had epidural.

We also collected some prospective trials from total hip and total knee replacement, thyroid surgery, lumbar disk surgery, oral surgery, cesarean section focused on postoperative VAS, narcotic consumption and so on. Abdulla et al. [9]. compared 120 patients into 4 groups, which received IV placebo (n = 30), IV parecoxib 40mg (n = 30), IV Metamizol 1g (n = 30), IV acetaminophen 1g (n = 30) after thyroid surgery in PACU. All study drugs were dissolved in 100 ml saline given over 15 minutes via IV infusion. Ten minutes before extubation, 2 mg piritramide was injected in all groups. Piritramide was also used as patient-controlled analgesia (PCA) pump in the postoperative period.

All groups had similar age, gender, BMI, ASA class. VAS scale was recorded every 2h for the first 6 hours as well as comparison of postoperative piritramide consumption. Results showed VAS at 2h after surgery was significantly less in the IV parecoxib and metamizol group compared with NaCl (P = 0.003; P = 0.005). While VAS at 4h, IV parecoxib is obviously lower than NaCl group and acetaminophen group (P = 0.001; P = 0.01). At the other side, VAS at 24h showed parecoxib group was higher compared with metamizol group and acetaminophen group (P = 0.008; P = 0.003). Piritramide consumption showed no significant difference in all four groups. There was an event happening in metamizol group that one patient had a severe bleeding at surgical wound causing upper airway obstruction. Tunali et al. compared IV acetaminophen and IV Dexketoprofen on postoperative pain and morphine consumption after lumbar disk surgery. 10 Sixty patients were randomly divided into 3 groups, IV acetaminophen 1 g (n = 20), IV dexketoprofen 50 mg (n = 20), IV 0.9% saline (n = 20). All groups' medications were dissolved in 100 ml saline administered over 15 min via IV infusion. Morphine 100 mg was also given to all patients as PCA. Patients were assessed for pain at 0, 1, 2, 6, 12 and 24 hours postoperatively. Result presented VAS of IV dexketoprofen group was significantly lower (P = 0.01), while not in IV acetaminophen group (P = 0.21), compared with IV saline group. The morphine consumption was not statistically significant in all groups. Yue et al [26]. designed 2 studies about efficacy and speed of onset of pain relief of fast-dissolving (FD) acetaminophen on postsurgical dental pain. Study 1 enrolled 438 patients who were divided into 3 groups, IV FD-acetaminophen 1g (n = 121), IV FD-acetaminophen 500mg (n = 119), IV placebo (n = 60). In study 2, 401 patients enrolled also randomly into 3 groups, IV FD-acetaminophen 1g (n = 163), IV standard acetaminophen 650mg (n = 158) and IV placebo (n = 80). Study 1 and 2 both showed over 6 hours postoperatively VAS is lower significantly in IV FD-acetaminophen 1g group than IV placebo group (P < 0.0001). IV FD-acetaminophen 1g group had also a great effect than IV FD-acetaminophen 500mg (P = 0.0004) and acetaminophen 650mg (P = 0.0009). Standard acetaminophen 650mg group presented efficacy than placebo (P < 0.0001), while FD-acetaminophen 500mg group was not significantly effective as compared with placebo (P = 0.1307) for the 0 to 6 hours post dose period. Furthermore, IV FD-acetaminophen 1g demonstrated significantly more effect than placebo, FD-acetaminophen 500mg group and acetaminophen 650mg group at 0-2 hours and 0-4 hours. Time to onset of first pain relief for the FD-acetaminophen 1 g group was significantly shorter than FD-acetaminophen 500mg (15 vs. 22 minutes; P = 0.047), acetaminophen 650mg (15 vs.20; P = 0.031) and both group with placebo in study 1(P = 0.002) and study 2 (P < 0.0001). Ayatollahi et al [27].designed a study to assess effect of preoperative IV acetaminophen in and after cesarean section under general anesthesia. Comparison of hemodynamic variables after intubation and VAS after surgery were also demonstrated. Sixty patients were randomly divided into 2 groups, IV acetaminophen 1g (n = 30) and IV placebo saline 1cc (n = 30). Study drug were dissolved in 500ml saline used at 20 min before anesthesia induction over 15 min via infusion. SBP, DBP, MAP, HR were recorded before laryngoscopy, immediately after laryngoscopy and in 1min, 5min after intubation, while VAS in 0h, 2h, 6h, 12h after surgery were also recorded, as well as neonatal Apgar score at 1-min, 5-min. Study result showed that in IVA group, all parameters were significantly lower than IV group saline (P < 0.05) but MAP immediately after laryngoscopy was not statistically difference (P = 0.134). VAS at 0h, 2h, 6h, and 12h after surgery in the IV acetaminophen group was lower than IV saline group respectively (P = 0.0001; P = 0.0001; P = 0.0001; P = 0.019). Rescue pethidine consumption at 2h, 6h after surgery were also significantly lower in IV acetaminophen group than IV saline group (P = 0.002; P = 0.001). However, there was no statistical difference compared with IV saline group 12h after surgery (P = 0.0236). There was no difference between two groups in 1-min and 5-min neonatal Apgar score (P = 1.00). Similarly, Alipour et al. compared the hemodynamic changes by IVA, ondansetron, granisetron, magnesium sulfate and lidocaine drugs after propofol with 336 patients who underwent elective orthopedic surgeries in Educational Hospitals of Mashhad University. Hypotension was less in IVA group (minute 1, P ≤ 0.001, minute 3, P = 0.027 and minute 10, P = 0.011) [28]. Khalili et al compared effect of preemptive and preventive acetaminophen on postoperative pain in patients undergoing lower extremity surgery under spinal anesthesia. 75 patients were randomly allocated into 3 groups, preemptive IV acetaminophen 15mg/kg (n = 25), preventive IV acetaminophen 15mg/kg (n = 25), IV placebo / saline (n = 25). All studies medications prepared in 100ml saline 0.9% were given to patients via infusion. Study medications were given 30 min before spinal puncture randomly (acetaminophen/placebo), and 30 min before skin closure (acetaminophen/placebo). Comparison of VAS at 6h, 12h, 18h, 24h after surgery, total postoperative meperidine consumption and time to first postoperative request for analgesic were presented. Result demonstrated that 25 (100%) patients in saline group, 19 (76%) patients in prevent group, 17 (68%) patients in preemptive group received rescue drug (P = 0.01). Total meperidine consumption was higher in saline group than preemptive group (42mg vs. 23mg; P = 0.003). However, there was no statistic difference between prevent group and saline group (P = 0.08). Meperidine used postoperatively was less in preemptive group than preventive group, but it was not statistically significant.

Time to first postoperative request for analgesia is statistically longer in both preemptive and preventive group than saline

group (P = 0.008). VAS in 6 hour after surgery was significantly lower in both preemptive and preventive compared with saline group (P < 0.001) while not statistically significant in 12h, 18h, and 24h after surgery in the three groups.29Among these studies, just one study designed that all subjects underwent only spinal anesthesia [29]. others all designed that patients underwent general anesthesia or spinal anesthesia. All studies showed VAS of group IV acetaminophen was lower than IV placebo statistically over 24h after surgery, especially in the first 4-6 hours. 6 studies except Abdulla et al 9 and Tunali et al 10 reported opioid consumption was significantly different between IV acetaminophen group and placebo in 24hour after surgery. In both their studies, opioid consumption was less in IV acetaminophen group, but not statistically different. Faiz et al. compared 80 patients who received IVA or ketamine randomly in postoperative pain at 4h, 6h, 12h, and 24h after abdominal hysterectomy. IVA group presented advanced pain free at each time (P < 0.05). In addition, this group needed significantly fewer rescue analgesic (P = 0.039) [30]. There was a new prospective, randomized, double-blind clinical trial published in 2017 which pointed out that as one part of multimodal analgesic, IV acetaminophen didn't present the advantage compared with the PO formula or the placebo group. There were totally 174 patients enrolled in this study after TKA. It was similar about the VAS and opiate consumption between IV group, PO group and placebo group in the first 6 hours and 24 hours after procedure. 11 However, all subjects received a peri-capsular injection of 300mg ropivacaine, 30mg ketorolac, 0.08mg clonidine, and 1mg epinephrine in a total volume of 0.9% saline. In addition, all patients received IV dexamethasone (4mg-10mg) prior to surgery.

PEDIATRIC

Patent ductus arteriosus (PDA), which happened in 70% infant born before 28 weeks postmenstrual age, required medical and surgery therapy [31]. Indomethacin and Ibuprofen, as prostaglandin synthesis inhibitor, were commonly used in clinical practice because of the risk of surgery. A Canadian retrospective research demonstrated 28% required treatment of PDA; 8% need surgery therapy, Seventy-five percent were treated with indomethacin alone, 17% required both indomethacin and surgical ligation in total 3779 patients. Infants with lower birth weight were more likely to be treated surgically [32]. However, PGI is associated with side effect including bleeding and platelet dysfunction based on both COX1 and COX2 inhibition. There were 5 cases reported by administration of enteral Acetaminophen in infant with PDA. All ductus closed in 1 week. Yet, no evidence showed Acetaminophen increased bleeding tolerance.33 Analogous studies and reviews also supported Acetaminophen was safe and effective in PDA. [34-40]. Nonetheless, all studies above demonstrated oral Acetaminophen not IVA. We need more evidences to prove IVA will be safe and effective in PDA.

Oral Acetaminophen was commonly used for treatment of fever in pediatric, while IVA was proved to be effective in fever as well. Dokko in 2015 reviewed and applied current data in evaluating whether or not children with cancer can safely benefit from IVA use. He found IVA was safe and effective in fever control [41]. A randomized, double-blind, placebo-controlled clinical trial, 80 children, aged 1-12 years, presenting for open heart surgery were entered in the trial and randomly allocated into two groups: Placebo and 15mg/kg IVA. The mean axillary temperature during first 24 h after operation was significantly lower in IVA group compared with placebo group (P = 0.001). Overall fever incidence during 24 h after operation was higher in placebo group compared with IVA group (P = 0.012) [42].

Treatment for pain after Pediatric surgery is crucial because of the biopsychosocial nature of pain [43]. Reduction of the rate of opioid-induced respiratory depression became more important. Tonsillectomy is commonly performed in pediatric patients. In 2006, an estimated 530,000 tonsillectomies (with or without adenoidectomy) and 132,000 adenoidectomies (without tonsillectomy) were performed in children younger than 15 years of age in the US. [44] Recently, more and more evidence showed IVA should be popular in this pediatric surgery. Subramanyam et al. reviewed the pain control children aged <17years after tonsillectomy with or without adenoidectomy. They found IVA in conjunction with morphine could reduce the narcotic rescue (3.3% fewer rescue events) and decrease the cost ($17.12) compared with opioid-alone strategy [45]. Similar with another randomized trail, 84 patients aged 4 to 13 years undergoing tonsillectomy were divided into 2 groups, to compare the analgesic effect of Dexamethasone versus IVA. However, IVA didn't show advantage compared with Dexamethasone [46]. Sajedi et al designed a randomized trial to compare oral acetaminophen and IV dexamethasone or combined for pain control and prevention of agitation after extubation in total 124 pediatric patients underwent Adenotonsillectomy. Median of pain score at 0, 10, 20 and 30 min after extubation were different between each study group with the control group (P < 0.001, 0.003 respectively); Median of agitation score in 0, 10, 20 and 30 min after extubation were different between each study group with the control group (< 0.001). The result demonstrated oral acetaminophen and IV Dexamethasone were both more effective than placebo for pain control and prevention of agitation. The combined formulation was superior to acetaminophen or dexamethasone separately. [47] Although this trial formulation is oral acetaminophen not IVA, the result pointed a new issue that combined formulation of acetaminophen and dexamethasone should be more effective and reduce

the adverse effect. Haddadi et al. compared IVA and rectal acetaminophen in paediatric patients after adenoidectomy. On 4 and 6 hour time intervals, pain in rectal acetaminophen receiving group was less than that in IV acetaminophen receiving group ($P < 0.05$). Demand for additional analgesic medication in rectal acetaminophen receiving group was less than that in IV group ($P = 0.0001$) [48]. Result showed rectal acetaminophen was superior. However, there were just 96 patients enrolled in this study and no placebo group.

In other surgeries for paediatric patients, IVA was also studied recently. A prospective randomized controlled trial in 45 healthy children compared IVA and oral acetaminophen. After surgery, IVA group received less opioid (272.9; 202.9-342.8 μg/kg) than control patients (454.2; 384.3-524.2 μg/kg; $P < 0.002$), while the opioid consumption of oral acetaminophen group (376.5; 304.1-448.9 μg/kg) was not significantly different with either IVA group ($P = 0.11$) or placebo group ($P = 0.27$). During the ward phase of care, IVA had better analgesia than control ($P = 0.002$), and both intravenous and oral group patients received less opioid than control ($P = 0.01$) [49]. In recovery room, IVA superior to control group, while oral group was no more effective than placebo group. IVA group presented less opioid consumption than oral group with no statistical significance. After recovery room, IVA and oral acetaminophen both showed less opioid consumption than placebo group. One limitation of this study is the small number of patient enrolled (45 subjects).

Regional anesthesia

There were limited studies showed IVA was used with local anesthetics in regional anesthesia. A recent randomized trial compared 3mg/kg IVA and 50mg/2ml dexketoprofen trometamol added in 3mg/kg 2% lidocaine in regional Intravenous Anesthesia. Comparison in hemodynamic effects, motor and sensorial block onset times, intraoperative VAS values, and analgesia requirements was presented. IVA with lidocaine group and dextoprofen with lidocaine group were both shorter in sensorial and motor block onset than lidocaine group ($P < 0.05$). VAS value was high in the group lidocaine than others ($P < 0.05$). There was no significant difference between group IVA and dextoprofen. There was also no significant difference between the groups in terms of heart rates and mean arterial pressures [50]. The similar study by Sen also supported this issue [51]. IVA offered a new choice to regional anesthesia as an adjuvant with local anesthetic.

DISCUSSION

The acceptance and use of IVA remains highly variable from institution to institution. While some hospitals have the medication on formulary, many do not and several hospitals have removed IVA from formulation mostly due to cost. The cost of IVA when first introduced exceeded $30 for one gram, while one gram of oral acetaminophen is less than 10 cents. The cost has since dropped to around $14 at most medical centers, but this still remains several hundred folds higher than the oral counterpart. With cost becoming a major focus in healthcare, it is understandable when institutions have reservations about making IVA readily available for physicians to prescribe to their patients.

IVA was studied popularly in adult acute pain control postoperatively, pediatric fever, pediatric acute pain control postoperatively, cardiac surgery and regional anesthesia. About the safety, no evidence showed any serious adverse effect after administration of IVA by normal dose. The controversy presented mainly in the effectiveness. Some studies didn't indicate what type of anesthesia the subject underwent. In general anesthesia, the time of opioid used in procedure, total dose of narcotic consumption during procedure, the onset and lasting time of narcotic (long-act agent or short-act agent) all affect the pain score postoperatively. In spinal or epidural anesthesia, the dose and concentration affect the time of anesthesia wearing off. It was also not indicated any nerve block combined and any medication for pain free added. Different trauma has different pain, while different surgeon makes different trauma. Some studies didn't indicate if all subjects underwent procedures by same surgeon. The category of surgery is also important. In surgery with mild or mild-moderate pain, IVA presented the advantage. Some studies didn't set up placebo group. Some studies designed with not enough subjects. In conclusion, IVA as a new choice in clinical practice, the advantages of which has been previously presented. But we need more and more effective evidences to prove it.

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