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An Investigation of Safety and Efficacy of Intravenous Paracetamol in Pain Management Following Cardiac Surgery

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ABSTRACT

Introduction: Optimum pain management immediately after surgeries can lower the possibility of pain syndrome and its following consequences. Opioids are amongst the analgesics used for postoperative pain control; however, their application can bring about several adverse effects. In this study, all the published articles regarding efficacy of Paracetamol in post-cardiac surgery pain management were systematically reviewed.

Materials and Methods: Pubmed and Scopus were searched for relevant articles. The employed search strategy was as follows: (Paracetamol OR Acetaminophen OR Propacetamol) AND (pain OR analgesia) AND coronary. All the English-language articles (with no time restriction), investigating the effectiveness of Acetaminophen in comparison with other analgesics or placebo, were included in the study. All the articles examining the efficacy of Paracetamol in combination with other analgesics were excluded from the search results.

Results: On the whole, our electronic search retrieved 192 articles from PubMed and 365 articles from Scopus. After screening the titles, abstracts, and full texts of the search results, only 5 English-language articles met our inclusion criteria.

Conclusion: Although Paracetamol demonstrated considerable efficacy in minimizing application of post-operative opioids, its strength in soothing post-operative pain is not significantly different from opioids. Further, conducting randomized-controlled-trials with large sample size are necessary to accurately reveal the efficacy of Paracetamol in curtailing application of opioids in post cardiac surgeries.

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Introduction

Cardiac surgery results in severe postoperative pain which can lead to emergency visit or readmission. Postoperative pain, if not treated properly, is a major factor that can negatively affect the outcome of surgery. Postoperative pain following cardiac surgery can affect pulmonary, cardiac, gastrointestinal, musculoskeletal, endocrine, and psychological functions and leads to atelectasis, pneumonia, tachycardia, increased O_2 consumption, muscle weakness and disuse, hyperglycemia, depression, and even chronic intractable pain (1). The incidence and prevalence of acute or chronic postoperative pain following cardiac surgery depends on a number of factors such as adopted pain measurement method, pain evaluation timing or evaluated population. Disparate reports have been provided on the intensity of postoperative pain based on resting condition or coughing.

Visceral, musculoskeletal, or neurogenic are the three major sources of post cardiac surgery pain. Myofascial structures such as muscles, bones, tendons, and ligaments are the main origins of postoperative pain. Postoperative pain can strike as burning or lancinating, and pain will grow stronger at night or by stretching

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the affected nerve. This type of pain can also be associated with the fascicular muscle twitching or spasm, hyperesthesia, paresthesia, or dysesthesia (2).

Both acute and chronic post cardiac surgery pain have demonstrated various risk factors. Patients aged under 60 years, long surgery duration and surgery site are among the determining risk factors for acute post cardiac surgery pain. However, major surgeries, operation time longer than 3 hours, ASA grade greater than III, depression and psychological vulnerability, high levels of stress but not neuroticism, female gender, low education, race, surgeon, and patients with extremely intense acute pain are the proposed risk factors for postoperative chronic pain (3). It has also been propounded that not only patients' attitudes and believes can affect the incidence of chronic pain, but also hospital structure, administrative anxiety, and believes of all hospital staff are likely to influence the intensity of patients' pain.

Various issues should be taken into account while implementing pain management strategies namely, regular and systemic screening, application of multimodal analgesics to lessen the possibility of side effects and specific drug levels.

Opioids, Paracetamol , Nonsteroidal anti-inflammatory drugs (NSAIDS) and anticonvulsants are commonly used for the purpose of postopera-tive pain management. Codeine, on the other hand, is not prescribed anymore for reasons such as decreasing potency, short action duration, and adverse side effects (4).

Opioids have traditionally been used as the main analgesic for postoperative pain management; however, they can cause a variety of debilitating side effects including excessive sedation, respira-tory depression, biliary spasm, depression of gastrointestinal motility, and postoperative nausea and vomiting (PONV). Based on the surgery type, opioids can be used in combination with different medications to reduce their adverse effects. NSAIDs as non-opioid candidates can be administered in some surgeries to reduce the adverse effects of opioids; however, they cannot be used in cardiac surgeries and cardiopulmonary bypass (CPB) due to the possibility of postoperative bleeding and renal dysfunction.

Acetaminophen (Paracetamol), has been proposed as a substitute for NSAIDs following cardiac surgeries due to its milder side effects on platelet condition and renal. The aim of this review was to study the articles regarding the efficacy of the Paracetamol in postoperative cardiac surgery pain management.

Materials and Methods

PubMed and Scopus as the main databases for retrieving relevant articles were searched. The literature search strategy was a follows: (Paracetamol OR Acetaminophen OR Propacetamol) AND (pain OR analgesia) AND coronary.

The inclusion criterion was selection of all the randomized human studies on efficiency of Paracetamol (alone not in combination with other analgesics). All the experimental studies, letters, short surveys, and editorials were omitted from the search results. All the studies which surveyed the analgesic value of Paracetamol in combination with other analgesics were also excluded from the search results as well.

The initial search results were screened based on their title and abstract. Relevant articles were selected for full text review. The most relevant articles were included in this systematic review and their citations were also searched for the possibility of missing any relevant article.

The procedure for selecting the relevant articles is demonstrated through a diagram in Figure 1. Moreover, detailed information is extracted from the included articles and presented in Table 1.

Results

After the initial search, 192 articles were retrieved from PubMed and 363 articles from Scopus, from which five articles were carefully selected as the most relevant articles which were presented in the both databases.

In some of the included studies, visual analog scale (VAS) was used for scaling postoperative pain intense. According to this scaling tool, 0 cm shows no pain and 10 cm shows the worst imaginable pain. In some other studies, on the other hand, the verbal rating scale (VRS): (0=no pain, 1=mild, 2=moderate, 3= intense, 4=very intense) was used for the evaluation of postoperative pain degree.

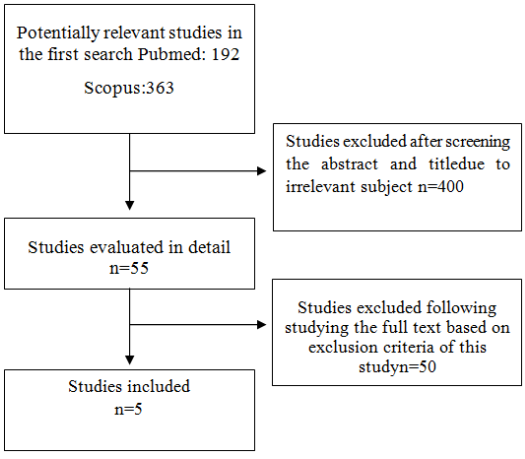

Figure 1. Alveolar dead space ROC curve

Table 1. Detailed data extracted from the reviewed articles

Author/ year	Patients	Drug doses	Pain scale	Operation	Results	Outcome	Randomization method/ similar groups/groups treated the same/
Ranucci, 1999(5)	Gr1:Paracetamol :20 Gr2: ketorolac:20 Gr3:tramadol:20	Gr1: 2 g IV Gr2: 60 mg IV Gr3: 200 mg IV	5-item verbal scale	Cardiac surgery	Ketorolac and tramadol were better option than Propacetamol	Gr1 showed higher rate of pain than Gr2 and Gr3	-
Avellaneda , 2000(6)	Gr1:Paracetamol :22 Gr2: metamizol:27 Gr3: ketorolac:23	Gr1: 1 g IV Gr2: 2 g IV Gr3: 30 mg IV	VRS	Aortocoron-ary bypass and valve replacement	Pain at baseline vs. after 60 min (Mean VRS): Gr1(1.41±0.26 vs. 0.64±0.16) Gr2(1.22±0.19 vs. 0.30±0.009) Gr3(1.59±0.21 vs. 0.38±0.12)	Pain was reduced in all the examined groups	Rotary system/Y/Y
Jahangiri Fard 2014,(7)	Gr1:Paracetamol :50 Gr2:Remifentanil :50	Gr1: 15 mg/kg Gr2: 100 µg/h bolus of 25 µg and lockout time of 15 minutes	VAS	CABG	VAS (8 hr): Gr1 vs. Gr2: 1.08 ± 1.92 vs. 0.28 ± 0.60 VAS(18 hr): Gr1 vs. Gr2: 1.04 ± 1.80 vs. 0.30 ± 0.78	Both groups showed effective pain reduction	Envelope technique/Y/Y
Lahtinen, 2002, (8)	Gr1:Propacetamol:40 Gr2:Placebo:39	Gr1: 2 g of Propacetamol hydrochloride in 100 mL normal saline Gr1: infusion of 100 ml normal saline All patients received 12 doses of study drugs at 6-h intervals (i.e., for 72 Postoperative h).	VAS	CABG	Oxycodone total (mg) Gr1: 141.8±57 Gr2: 123.5±51.3 Rescue oxycodone (mg) Gr1: 6.0±4.9 Gr2: 5.1±4.7 Number of patients who received rescue oxycodone (n) Gr1: 30 Gr2:27	Opioid consumption was smaller in Gr1 compared with Gr2 G1 did not enhance the analgesia compared with Gr2	Random numbers/Y/Y
Pettersson, 2005,(9)	Gr1 and 2: Acetaminophen	GR1:1g of Acetaminophen as tablet Gr2: 1 g Acetaminophen IV (every 6 hr after surgery)	VAS	CABG	Opioid consumption: Gr2 vs. Gr1 (17.4 mg ±7.9 mg vs. 22.1 mg ±8.6 mg)	No difference in VAS between groups.	Envelope technique/Y/Y

Results

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Discussion

Sufficient analgesia immediately after operation is an indicator of good prognosis of pain syndrome and its consequences.

The potential of multimodal or balanced analgesia in managing the postoperative pain was determined for non-cardiac surgeries. It was found that Paracetamol and NSADs can be applied in combination with opioids in balanced analgesia to reduce the opioid-associated side effects. By dint of applying these combinations of analgesia, the possibility of inducing analgesic effect through different mechanisms is raised.

Paracetamol is a safe non-opioid analgesic which is used for postoperative pain management. The onset of analgesia is 5-10 minutes and its half-life is 1-4 hours without the reported side effects for opioids. Regarding cardiac surgeries, nevertheless, there is no ideal postoperative pain management strategy that can relieve the pain associated with sternotomy, leg vein harvesting, pericardiotomy, and chest tube insertion without potential adverse effects.

Analgesic effect

Reducing opioid consumption

Opioids are the most frequently used analgesics for providing postoperative relief.

One placebo-controlled study was carried out on the advantages of Propacetamol in post-cardiac surgery to diminish the administration of oxycodone. Propacetamol could not significantly curtail the need for opioid administration. However, the authors pointed out that propaceta-mol could lead to 30% decrease in post-cardiac surgery oxycodone requirement; however, this reduction did not clinically decrease pain score, patient satisfaction, or respiratory function variables within 72 hours after cardiac surgery (8).

In another recent study, the efficacy of Paracetamol was compared with Remifentanil which is an ultra-short-acting opioid metabolized by non-specific esterase.(7). According to that study, although both medications could effectively ameliorate the postoperative pain during the first 24 hours, paracatemol resulted in lower mean VAS

scores as compared with Remifentanil especially during 8-18 hours after surgery.

A number of studies considered the efficacy of the Paracetamol following gynecologic and orthopedic surgeries showing that Paracetamol has acceptable potential in lessening postoperative morphine and ketorolac administration (10, 11).

Paracetomal administration has been proposed to have morphine-sparing effect at 72 hours following spinal fusion surgery (12). Despite the mentioned studies, in some clinical trials Paracetamol did not show opioid-sparing effect and its application did not cut down the consumption of morphine following vertebral disk surgery and total hip or knee replacement (13, 14). Paracetamol is also proposed to have better analgesic effect at severe pain degrees as compared with moderate degrees of pain (8). Therefore, the opioid-sparing effect of Paracetamol following cardiac surgery was not revealed.

Administered analgesic dosage

According to the study of Lahtinen et al., the administered dosage of the Propacetamol with respect to the pain intensity might be an influential factor. Although based on the literature, 2 g at six-hour intervals is suggested as the maximum dose which should be applied, the association between effective analgesic concentration and the optimum dose for application is yet to be found.

In a study examining the efficacy of three non-opioid drugs including metamizol, ketorolac, and Propacetamol, it was found that although pain degrees were lowered in all the experiment groups, the efficacy of Propacetamol was less than other medications, which might be due to the small administered dose of Propacetamol (1 g).

Analgesic mechanism

Based on the previous studies, Paracetamol has low inhibitory effect on cyclooxygenase and no anti-inflammatory effect. However, the main action of non-opioid analgesics is blocking the peripheral synthesis of cyclooxygenase 1 and 2 through inhibition of prostaglandin synthesis. Prostaglandin synthase is involved in producing vasodilator prostaglandins including PGI2 (prostacyclin) leading to blood pressure reduction as a result of a decrease in systemic vascular resistance and the consequent cardiac output elevation.

It has been supposed that Paracetamol has direct effect on central nervous system and its analgesic effect can be mediated through central nervous system and its cerebrospinal fluid concentrations (15). In a study done by Avellaneda et al, Propacetamol caused mild hypotension (which is supposed to be secondary to inhibition of adrenergic activity) while relieving the postoperative pain. Nevertheless, this hypotensive effect did not result in clinically relevant decrease in cardiac contractility (6).

Administration route

The optimum route for Paracetamol administration following cardiac surgery is not clear. In one prospective, randomized, double-blind, placebo-controlled project studying the efficacy of Paracetamol in combination with NSAIDs, rectal route was chosen instead of oral administration.

Oral administration of Paracetamol , on the other hand, has been shown to result in a wide range of individual plasma concentrations of the analgesic. It is also suggested that the absorption of these analgesic medications might be varied in the first 24 hours following oral administration (16); pyloric closure is proposed to be responsib-le for impaired absorption. In various studies, oral administration of Acetaminophen is curbed due to factors leading to impaired absorption of medication including: preoperative fasting, long-lasting anesthesia and gastric emptying (17).

Lahtinen et al. showed that intravenous application of 2 g of Acetaminophen prodrug after cardiac surgery could reduce the opioid consumption (8). The efficacy of postoperative intravenous route for Acetaminophen application has recently been under the investigation.

In a recent study, the mean opioid consumption of patients with intravenous Paracetamol administration was lower than those with oral Paracetamol application (9). This result was also confirmed following orthopedic and laparoscopic surgery in which intravenous Paracetamol could reduce the consumption rate of opioids (18, 19). Although the opioid-sparing effect of acetaminop-hen is not clearly revealed, short lasting peaks of high plasma concentrations can be achieved following intravenous application.

Conclusion

There have not been enough clinical trials on the efficacy of Paracetamol administration in post-cardiac surgery pain management. Despite the aforementioned articles, the opioid-sparing effect of Paracetamol used in cardiac surgery is not well-established in the body of literature and the results of the studies are conflicting. Further, large sample sized placebo-controlled studies are mandatory for more reliable results regarding the strength of Paracetamol as an alternative for opioid analgesics.

Conflict of Interest

The authors declare no conflict of interest.

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