Asian Journal of Medical and Pharmaceutical Sciences

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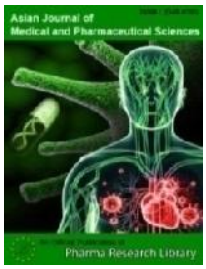

R E S E A R C H A R T I C L E

Assessment of Pain Relief and Tolerability of Cyclo-Oxygenase-2 Inhibitors as Post-Operative Analgesics

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A B S T R A C T

Background and objectives: Pain is an unavoidable outcome of every surgery, and most of the time it is sub- optimally treated. Conventional postoperative analgesics are opioids and non-selective NSAIDs, which have moderate to severe adverse effects profile. Parecoxib is the only parenterally administered selective cyclooxygenase-2 inhibitor available. This study was done to assess the pain relief and tolerability of cyclooxygenase-2 specific inhibitor after giving first dose postoperatively. **Method:** This was a observational and comparative study between parecoxib 40 mg IV and diclofenac 75 mg IM as postoperative analgesic. After baseline score subsequent scores were taken at intervals of 30 minutes, 1, 4 and 8 hrs, after administering analgesic. Analgesic efficacy was assessed in terms of mean pain intensity score difference and tolerability assessment was done by monitoring general adverse events. Statistical analysis was done by using student't' test with $p< 0.05$ as significant. **Results:** 40 patients were enrolled in the study, 20 patients in each group. Demographic data was similar between two groups. Mean pain intensity score at baseline was 3.35 and 3.36 in parecoxib and diclofenac group respectively. The difference in pain score between the groups were not statistically significant ($p >0.05$) in total 8 hours of study. Reduction in mean pain intensity upto 50 % was achieved in 30 min and 1 hr in parecoxib and diclofenac group respectively. At the end of 8 hours, 15 (75 %) patients in parecoxib group experienced 'no pain'; while in diclofenac sodium group it was only with 8 (40 %) patients. Only mild adverse events like nausea, vomiting, and headache were present. **Conclusion:** The results of the study indicate that selective single dose of COX-2 inhibitor parecoxib sodium 40 mg IV is comparable to single dose of diclofenac sodium 75 mg IM Both the drugs are found to be equally and well tolerated as single dose postoperative analgesic.

Keywords: Parecoxib, Diclofenac, Cox-2inhibitor, PostoperativeAnanlgesic

A R T I C L E I N F O

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ARTICLE QR-CODE

A R T I C L E H I S T O R Y: Received 19 April 2018, **Accepted** 29 May 2018, **Available Online** 19 June 2018

Citation: *Sandeep Akkam, et al.* Assessment of Pain Relief and Tolerability of Cyclo-Oxygenase-2 Inhibitors as Post-Operative Analgesics.*A. J. Med. Pharm, Sci.*, 2018, 6(1): 32-40.

C O N T E N T S

1. Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Postoperative pain is an expected outcome for each person who undergoes surgery, the increased attention there is overwhelming evidence that pain in hospitalized patients remains sub optimally treated because pain has clinical, economic and human consequence, such as change in immune system function, decreased healing and diminished ability to function.

The drug therapy for treating postoperative pain involves opioids and non- opioid drugs. Non-opioid drugs mainly consist of non-steroidal anti-inflammatory drugs (NSAIDs), non selective Cyclooxygenase-1(COX-1) inhibitors and recently developed selective Cyclooxygenase 2 (COX-2) inhibitors.The three main types of opioid receptors that have been described so far are μ, δ and κ receptor. In the dosage range typically used to treat patients with acute postoperative pain, μ receptor agonists have no therapeutic ceiling effect. Therefore unlike non-opioid analgesics dosages of these drugs are adjusted upwards until satisfactory pain control is achieved or adverse effect become intolerable.

The adverse effect most commonly associated with opioids are respiratory depression, sedation, nausea, vomiting, constipation, urinary retention and itching. Other adverse effects include confusion, hallucination, nightmares, multifocal myoclonus and dizziness. These effects can adversely affect the ability to recuperate from a surgical procedure.

Opioid metabolites may also cause adverse effects, e.g. morphine 6- glucuronide, the primary active metabolite of morphine, may accumulate in patient with diminished renal function and contribute to adverse effects including cognitive impairment, myoclonus and hyperalgesia. Intramuscular (IM) opioids can provide effective analgesia but only if administered in the appropriate dose at appropriate intervals. The use of NSAIDs is one of the most common non-opioid analgesic approach currently used for management of postoperative pain.

NSAIDs inhibit the COX enzyme, which are involved in the synthesis of prostaglandins responsible for inflammation, pain and fever. The enzyme COX exists two iso-forms (COX-1 and COX-2). COX-1 mediates gastric mucosal integrity and renal and platelet function, while COX-2 is expressed after injury to contribute to inflammation and hyperalgesia.Non-selective NSAIDs blocks both the COX iso-forms (COX-1 and COX-2). Inhibition of COX-1 is associated with gastrointestinal and antiplatelet adverse events.The isolation of COX-1 and COX-2 enzymes has resulted in the development of exciting hypothesis that the therapeutic and adverse effects of NSAIDs could be uncoupled.

Parecoxib is the prodrug of valdecoxib, a selective COX-2 inhibitor, developed for parenteral administration. Approved COX-2 selective inhibitors such as, celecoxib, rofecoxib, and valdecoxib are only available for oral administration. Therefore, parecoxib is the novel option for acute postoperative management and may not produce adverse effects associated with non-selective COX inhibitors. In addition, postoperative patients with nausea and vomiting would benefit from an analgesic, anti-inflammatory COX-2 selective inhibitor available via the parenteral route.

The main goals of this study is,

1. Assessment of pain relief by measuring pain intensity before and after getting first dose of COX-2 inhibitor.
2. Tolerability assessment by monitoring the general adverse events.

Pathophysiology of Pain

Pain is an unpleasant sensation localized to a part of the body. It is often described in terms of a penetrating or tissue-destructive process (e.g., stabbing, burning, twisting, tearing, squeezing) and/or of a bodily or emotional reaction (e.g., terrifying, nauseating, sickening). Furthermore, any pain of moderate or higher intensity is accompanied by anxiety and the urge to escape or terminate the feeling. These properties illustrate the duality of pain: it is both sensation and emotion. When acute, pain is characteristically associated with behavioral arousal and a stress response consisting of increased blood pressure, heart rate, pupil diameter, and plasma cortisol levels. In addition, local muscle contraction (e.g., limb flexion, abdominal wall rigidity) is often present.

Central Pathways for Pain

The Spinal Cord and Referred Pain

The axons of primary afferent nociceptors enter the spinal cord via the dorsal root. They terminate in the dorsal horn of the spinal gray matter. The terminals of primary afferent axons contact spinal neurons that transmit the pain signal to brain sites involved in pain perception. The axon of each primary afferent contacts many spinal neurons, and each spinal neuron receives convergent inputs from many primary afferents. From a clinical standpoint, the convergence of many sensory inputs to a single spinal pain-transmission neuron is of great importance because it underlies the phenomenon of referred pain. All spinal neurons that receive input from the viscera and deep

musculoskeletal structures also receive input from the skin. The convergence patterns are determined by the spinal segment of the dorsal root ganglion that supplies the afferent innervation of a structure. For example, the afferents that supply the central diaphragm are derived from the third and fourth cervical dorsal root ganglia. Primary afferents with cell bodies in these same ganglia supply the skin of the shoulder and lower neck. Thus sensory inputs from both the shoulder skin and the central diaphragm converge on pain-transmission neurons in the third and fourth cervical spinal segments. Because of this convergence and the fact that the spinal neurons are most often activated by inputs from the skin, activity evoked in spinal neurons by input from deep structures is mislocalized by the patient to a place that is roughly coextensive with the region of skin innervated by the same spinal segment. Thus inflammation near the central diaphragm is usually reported as discomfort near the shoulder. This spatial displacement of pain sensation from the site of the injury that produces it is known as referred pain.

Ascending Pathways for Pain

A majority of spinal neurons contacted by primary afferent nociceptors send their axons to the contra lateral thalamus. These axons form the contralateral spinothalamic tract which lies in the anterolateral white matter of the spinal cord, the lateral edge of the medulla, and the lateral pons and midbrain. The spinothalamic pathway is crucial for pain sensation in humans. Interruption of this pathway produces permanent deficits in pain and temperature discrimination. Spinothalamic tract axons connect to thalamic neurons that project to somatosensory cortex. This pathway from spinal cord to thalamus to somatosensory cortex appears to be particularly important for the sensory aspects of pain, i.e., its location, intensity, and quality. Spinothalamic tract axons also connect to thalamic and cortical regions linked to emotional responses, such as the cingulate gyrus and frontal lobe. This pathway is thought to subserve the affective or unpleasant emotional dimension of pain.

Pathophysiology of Postoperative Pain

Surgery represents a form of premeditated injury to the body. We understand that surgical injury provokes changes in the peripheral and the central nervous system (CNS) that must be dealt with therapeutically to define effective care and to positively influence outcome. The physical processes of incision, traction, and cutting of tissue stimulate free nerve endings and specific nociceptors. The threshold for activation and the activity of these receptors is modified by the local release of chemical mediators of inflammation and sympathetic amines released within the surgical stress response. Substances such as bradykinin, serotonin, and histamine both sensitize and stimulate the receptors, whereas arachidonic acid derivatives only sensitize them. The influence of the sympathetic nervous system is appreciated, though the exact mechanisms of its interaction are not well defined. Problem 1 in postoperative pain is this peripheral sensitization, which is characterized by the decreased activation threshold of receptors, a shortened response latency to the point that there can be spontaneous pain (pain without an obvious stimulus), and an exaggerated response within the peripheral nervous system to a given stimulus (i.e., the patient stays in pain long after the surgeon has examined the healing incision).

Clinically, the patient manifests primary hyperalgesia, meaning that even gentle stroking of the incisional area causes exquisite pain. Secondary hyperalgesia results when the elaborated chemicals and vascular response sensitize adjacent receptors such that pain spreads, i.e., the patient's skin is painful and sensitive to evenlight touch away from the incision. Ordinarily, A-d and c-fibers transmit nociceptive information from the periphery to the CNS. The input from A-d fibers is associated with sharp, localized pain that is rapidly conveyed (because these fibers are myelinated), whereas that related to the c-fibers is usually aching, throbbing, diffuse, and more slowly transmitted (because these fibers are unmyelinated). A-d and c-fibers make up about 70%–90% of a peripheral nerve. What percentage function under normal circumstances and what percentage act as "reserve cabling" (so-called silent primary afferent fibers) is not known. Problem 2 relates to the reality that A-a and A-b fibers can be induced to carry nociceptive input to the CNS when peripheral sensitization occurs.

This input does not necessarily undergo the usual inhibition in the dorsal horn, as does A-d or c-fiber input, because A-a and A-b fibers do not terminate in the same levels of the dorsal horn (the substantia gelatinosa), as do the A- d and c-fibers. An ancillary problem that is a consequence of these two problems is that there is a constant bombardment of the CNS with noxious input: this overwhelms the CNS's innate capability to filter or ameliorate painful input and fuels ongoing plasticity in the CNS response. Problem 3 occurs when the noxious input begins to be processed by the CNS. Spinal reflexes (which require no integration of input within the CNS), such as muscle spasm and sympathetic stimulation, are provoked. Supraspinal reflexes that involve the integration of nociceptive input from a few spinal segments incite the mediators of the stress response. The surgical stress response (SSR) peaks in the postoperative period and has major effects on the cardiac, coagulation, and immune systems of the body. Although regional anesthesia and analgesia do not inhibit the local release of stress mediators into the bloodstream

Parecoxib

(N-[{4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl}sulphonyl] propanamide) is a sulphonamide-based prodrug that is hydrolyzed by hepatic microsomal carboxylesterase in vivo to valdecoxib, the pharmacologically active selective COX-2 inhibitor. Valdecoxib inhibits the isoform of prostaglandin endoperoxide synthetase (prostaglandin G/H synthetase) and exhibits anti-inflammatory, analgesic, and antipyretic activity. COX-2 is an inducible enzyme that is mainly found at sites of inflammation, yet is also produced constitutively in the brain, kidney, and reproductive organs. The active moiety of parecoxib exerts its analgesic effect through several proposed mechanisms. It may alter nociception by acting on prostaglandin production within the CNS, modulating neurotransmitter release. The

potential alteration of nociception occurs by prostaglandin synthesis of arachidonic acid, which is released from membrane phospholipids in response to inflammation. The COX pathway metabolizes unbound arachidonic acid to prostaglandin H2, which is the subtype known to increase the electrical excitability of sensory neurons and mediate bradykinin-induced hyperalgesia. A second proposed mechanism includes a direct action at an excitatory or inhibitory amino acid site. In addition, inhibition of COX-2 prostaglandin synthesis at sites of tissue inflammation may produce a peripheral and local analgesic effect.

Adverse Effects and Precautions

As for NSAIDs in general, hypersensitivity reactions, including anaphylaxis and angioedema and serious skin reactions, have been reported with valdecoxib and may therefore occur with parecoxib, a prodrug of valdecoxib. Parecoxib should be discontinued at the first signs of hypersensitivity. Some of these reactions occurred in patients with a history of allergic reactions to sulfonamides and the use of parecoxib is contra-indicated in such patients.

Parecoxib should be avoided in patients with severe hepatic impairment, inflammatory bowel disease, and moderate to severe heart failure. It should not be used in patients with a history of ischaemic heart disease or cerebrovascular disease. It should also not be used following coronary artery bypass graft surgery as there may be an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, stroke, renal impairment, deep surgical infections, and sternal wound complications. This may apply especially in obese patients or those with a history of cerebrovascular disease. Parecoxib should be used with caution in patients with significant risk factors for cardiovascular disease or peripheral arterial disease. Caution is also recommended when using parecoxib in dehydrated patients; rehydration may be advisable before giving parecoxib.

Diclofenac Sodium

Sodium [2-(2,6-dichloroanilino)phenyl]acetate

Administration

Diclofenac, a phenylacetic acid derivative, is an NSAID. It is used mainly as the sodium salt for the relief of pain and inflammation in various conditions. For the treatment of postoperative pain a dose of 75 mg may be given over 30 to 120 minutes. The dose may be repeated if necessary after 4 to 6 hours. To prevent postoperative pain, 25 to 50 mg diclofenac sodium may be given after surgery over 15 to 60 minutes followed by 5 mg/hour to a maximum of 150 mg daily. The maximum period recommended for parenteral use is 2 days. Diclofenac sodium is also used intramuscularly in renal colic in a dose of 75 mg repeated once after 30 minutes if necessary.

Precautions

Use of IV diclofenac is contra-indicated in patients with moderate or severe renal impairment, hypovolaemia, or dehydration; in addition, IV diclofenac should not be used in patients with a history of haemorrhagic diathesis, cerebrovascular bleeding (including suspected), or asthma nor in patients undergoing surgery with a high risk of haemorrhage

2. Methodology

It is an observational comparative study between parecoxib sodium 40 mg IV and diclofenac sodium 75 mg IM as postoperative analgesic, carried out in all the six units of surgery department. A day before surgery only those patients were short listed from the list of next day surgery, who fulfill the inclusion and exclusion criteria of the study. Recruitment of the patients was done on the basis of postoperative treatment chart whether the patient is going to receive the study medication (parecoxib sodium 40 mg IV OR diclofenac sodium 75 mg IM)

Study Criteria

Inclusion criteria:

- Patients of either sex undergone general surgery with age group 18 and above
- Patients who were given selective COX-2 inhibitor parecoxib sodium or diclofenac sodium as their first analgesic for postoperative pain, after recovering from anesthesia.

Exclusion criteria:

- Patient with clinically significant abnormalities on physical and laboratory examination.
- Patients with known hypersensitivity to NSAIDs.
- Patients who had gastric or duodenal ulcers and bleeding tendencies, significant renal impairment, and hepatic impairment.
- Patients on concomitant therapy with drugs such as warfarin, antiepileptic, fluconazole, and ketoconazole.

Source of data: All the necessary and relevant data were collected from

- ✓ In-Patient progress records
- ✓ Treatment charts
- ✓ Laboratory data reports
- ✓ Patient history record

Study Procedure

Data collection: An informed consent was taken from each patient before enrolling them into the study. The data was collected on the patient profile form and a self-generated proforma The patient's demographic data, current medications, laboratory investigation, past medical and medication history was collected from the patient's progress record, treatment chart, laboratory reports and patient history record The demographic data collected includes the patient's age, sex, and weight. The current medication data includes all the drugs, their dosage, route of administration with frequency, date of drugs started and stopped.The past medical and medication history data collected includes the patient's previous allergies, co-morbidities and the drugs received previously. The laboratory data collected includes the relevant laboratory investigations done to confirm the ADR.

Informed consent:

Written informed consent was taken from every patient, regarding their participation in the study.

Pain assessment:

Pain assessment was done through Visual Analog Scale (VAS) It is a simple 10 cm horizontal and straight line extending from "no pain" to the extreme limit of pain as defined by several phrases, e.g., "pain as bad as it could possibly be" or "worst pain I have ever experienced" or

"the worst pain I could imagine" or "agonizing pain."VAS are one of the most frequently used measurement scales in health care research. The VAS is most commonly known and used for measurement of pain.

Recommendations for VAS:

- If more than one variable or aspects of a concept is being measured using the VAS, use a separate sheet of paper for each scale. One rating should not be a reference point for the next rating.
- Use a computer generated line or have the VAS printed. Photocopying increases or decreases the size on some machines.
- Using gradations on the scale may reduce its sensitivity, depending on whether a horizontal, vertical or curvilinear scale is used.
- If more than one VAS is used to measure the same phenomenon, reverse the anchors at each end on some of the scales to reduce a response bias.
- If more than one ruler is used for manual scoring, make sure all rulers are identical.
- Make sure subjects have no visual or motor impairment.

The VAS scale used in the study was a simple 10 cm horizontal, straight, sharp, and dark black line. The line was kept non-graded to maintain the sensitivity. After shifting the patient towards from recovery room, postoperatively, they were explained about VAS i.e. they have to mark on a 10 cm long ungraded line representing no pain on the left end and goes on increasing as the line proceeds towards right side signifying agonizing pain, on most right hand side end. Subsequently the patients were asked, based on above explanation to mark on VAS according to pain intensity felt by them at that moment. After taking first pain score representing the baseline score, the patients were administered analgesics. First pain score after administering the analgesic was taken after 30 minutes, subsequent scores were taken at an intervals from the time of taking baseline scores, of 1 hr, 4 hr and 8 hrs. the patient were not allowed to take the reference of the previous score in order to maintain the sensitivity of the pain score. After assessing pain score the VAS was marked into 10 equal divisions and following grading were given to the VAS

- Little pain.
- Some pain.
- Mild pain.
- Moderate pain.
- Severe pain.

For the convenience of statistical analysis the subjective pain scores were converted into following numeric. 'No pain'= 0, 'Little pain'= 1, 'Some pain'= 2, 'Mild pain'= 3, 'Moderate pain'=4, 'Severe pain'=5, and 'Agonizing pain'= 6.

Statistical Analysis: Statistical analysis was done by student't' test with $p< 0.05$ as significant.

3. Results and Discussion

Patient:Total 40 patients were taken in the study according to their post-operative analgesic, 20 patients in each, parecoxib sodium 40 mg I.V. group and diclofenac sodium 75 mg I.M. group. There were 12 male and 8 female in parecoxib sodium group while diclofenac sodium group had 11 male and 9 female. The age of the patients in parecoxib sodium group ranged from 18-67 yrs with a mean of 38.9 yrs. In diclofenac sodium group age ranged from 22-64 yrs with a mean of 45.15 yrs. The weight of patients in parecoxib sodium group ranged from 43- 73 kg with a mean of 55.80 kg. In diclofenac sodium group weight ranged from 43-72 kg with a mean of 56.25 kg.Demographic data did not differ significantly between two groups.

Pain assessment:

Mean pain intensity score at baseline in parecoxib sodium group was 3.35 and in diclofenac sodium group was 3.6 which did not differ significantly. The difference in pain score between the groups were not statistically significant ($p >0.05$) in total 8 hours of study. After treatment, at 30 minutes mean pain score showed a reduction of 55.23 % with parecoxib sodium and 26.38 % with diclofenac sodium. At the end of 1 hour, fall was 79.1 % in parecoxib sodium group and 54.16 % in diclofenac sodium from baseline. At the end of 4 hours and 8 hours, fall in parecoxib sodium group was 89.55% and 92.53 % from Reduction in mean pain intensity up to 50 %, in parecoxib sodium group was achieved in baseline respectively, and similarly in diclofenac group fall in pain intensity was 83.33 % and 80.55 % at the end of 4 hours and 8 hours from the baseline respectively.30 minutes whereas the same was achieved in diclofenac sodium group in 1 hour. An increase in mean compared to 4th hour assessment. Pain intensity score was observed in diclofenac sodium group at 8th hour assessment.

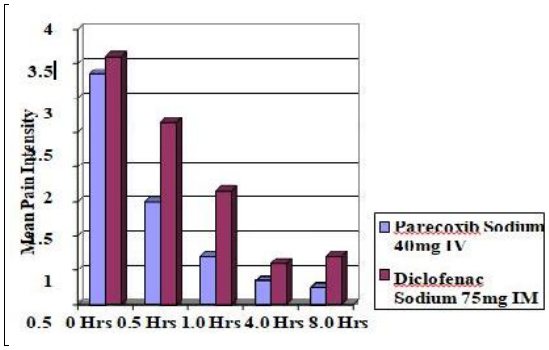

Figure 1: Mean pain intensity scores (VAS) over time

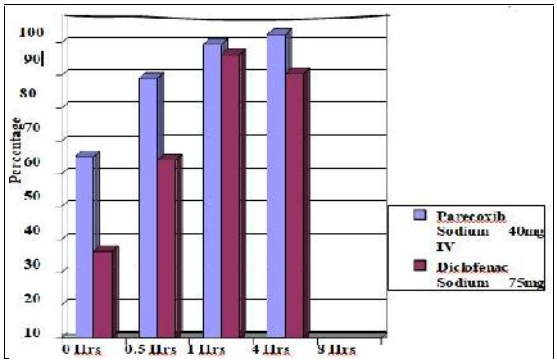

Figure 2: Percentage fall in pain intensity from base line

At the end of 8 hours, a good number, 15 (75 %) patients who received parecoxib sodium 40 mg IV experienced 'no pain', while in diclofenac sodium group it was only with 8 (40 %) patients.50 % of the total patients in diclofenac sodium group complained 'little pain' after 8 hours of treatment while only 25 % of the patients who received parecoxib sodium complained 'little pain'. No patients in the either group asked for rescue analgesic during the 8 hour pain assessment

Tolerability Assessment:

Only 20% of the total patient in parecoxib sodium group reported adverse events while 35% patients reported in diclofenac sodium group. Common adverse events, present in both group were nausea, vomiting, and headache. Only one patient reported dizziness in diclofenac group. No patient reported hypersensitivity in any group.

Discussion:

This study compared the analgesic efficacy and tolerability of single dose of parenteral, selective COX-2 inhibitor parecoxib sodium 40 mg IV with single dose of non selective COX inhibitor diclofenac sodium 75 mg IM as post-operative analgesic. Most of the patients in KLES hospital are prescribed diclofenac sodium 75 mg IM as post-operative analgesic. This was the reason to compare the analgesic effects of parecoxib sodium with that of diclofenac sodium. The results of the study do not show any significant difference in the mean pain intensity scores during the 8 hour pain assessment time between the two drugs. Parecoxib sodium was found comparable with diclofenac sodium in reducing pain intensity score. However the fifty percent reduction in the pain intensity in the parecoxib sodium group within 30 min shows its faster onset of action compared to diclofenac sodium. Also the larger number 15 (75 %) of patients recorded no pain after 8 hours of treatment in parecoxib sodium group. The finding of the study provides data regarding the question of the relative analgesic potency of COX-2 specific versus non selective COX NSAIDs. There was a study published parecoxib sodium 20 mg and 40 mg IM or IV, both doses were comparable to ketorolac 60 mg IM in time required for the onset of analgesia, but parecoxib sodium 40 mg had significantly longer duration of action. Another study found parecoxib sodium at least as effective as COX non-specific conventional NSAID ketorolac. In terms of the speed of onset of analgesia and the general magnitude of analgesia (degree of pain relief and pain intensity), IV parecoxib 20 &40 mg were comparable with IV ketorolac 30 mg, for managing acute post laparotomy pain. One more study concur with our results, in this parecoxib sodium was compared with proparacetamol (parenteral form of acetaminophen). VAS scores at rest and while coughing at 1st, 6th and 12th hours did not differ statistically between the treatment group. Although most of the placebo controlled studies parecoxib sodium has shown significant efficacy against placebo, it shows comparable effects with conventional non-selective NSAID in terms of pain intensity and pain relief. In a placebo controlled trail there was no significant difference found between the treatment groups in the pain intensity scores at rest and on deep inspiration. NSAIDs have opioid sparing effects and reduce the opioid consumption in post-operative analgesia. Also these NSAIDs are very much helpful in opioid related side effects. This study has shown the effects of parecoxib sodium in terms of reducing pain intensity, on the contrary this study lacks in assessing the efficacy of parecoxib sodium in having opioid sparing effects. Even many studies suggest that parecoxib sodium has opioid sparing potential, thereby reducing the opioid consumption and opioid related side effects.

Parecoxib sodium is a COX-2 selective inhibitor, which reduces the number of adverse events associated with non-selective COX-1 inhibition. These include upper gastrointestinal ulceration and bleeding, renal dysfunction and bleeding related to platelet inhibition.In this study both parecoxib sodium 40 mg IV and diclofenac sodium 75 mg IM as single dose for postoperative analgesic, were safe and well tolerated as most of the adverse events in each group were mild in intensity. There were no serious or severe adverse events reported in any of the group. This study also concurs with the previously published studies in terms of tolerability assessment of parecoxib sodium. With the advent of voluntary withdrawal of rofecoxib by Merck in Sep2004, followed by withdrawal of valdecoxib by Pfizer in April 2005 due to serious cardiovascular events, there has been an increase concerns on the use of COX-2 specific inhibitors. Several studies has strong evidence related to thromboembolic risks associated with COX-2 inhibitors. In a study, assessing the safety of valdecoxib and parecoxib in patient undergone CABG they found that, while this drug combination is efficacious in reducing pain it may expose vulnerable patients to additional cardiovascular risk. Another trial tested safety of sequential parecoxib and valdecoxib in controlling post CABG pain. The authors concluded that the chance of experiencing adverse cardiovascular events was significantly higher in COX-2 inhibitors compared to placebo. The limited period of evaluation was not long enough to determine the potential differences between the two drugs for complication rates and in clinically relevant outcomes, such as resumption of physical activity. In this study we did not measure the time course of postoperative recovery.

Table 1: Demographic characteristics of patients

Patient	Parecoxib Sodium(n=20)	Diclophenac sodium(n=20)
Sex M/F	12/8	11/9
Age	38.9 ±13.26	45.15±13.55
Weight	55.80 ±7.88	56.25±9.35

Results are expressed as Mean ± SD

No difference between the groups

Table 2: Types of Surgeries

Surgery	Parecoxib Sodium		Diclophenac sodium	
	Male	Female	Male	Female
Cholecystectomy	2	3	2	1
Hernia (Mesh repair)	5	0	8	3
Appendectomy	1	0	0	0
Total abdominal hysterectomy	0	0	0	2
Spleenectomy	0	0	0	1
Colostomy closure	1	0	0	0
Fibroadenoma breast excision	0	1	0	1
Cystrogastronomy	1	0	0	0
Adrenalectomy	1	0	0	0
Pilonidal sinus excision	0	1	0	0

Table 3: Mean Pain Intensity Scores

Time (Hrs)	Parecoxib Sodium	Diclofenac Sodium
0	3.35 ± 1.13	3.6 ± 0.59
0.5	1.5 ±0.68	2.65 ± 0.67
1.0	0.7 ± 0.57	1.65 ± 0.67
4.0	0.35 ± 0.48	0.6 ± 0.59
8.0	0.25 ± 0.44	0.7 ± 0.65

Results are expressed as Mean ± SD p> 0.05 (No significant)

Table 4: Percentage fall in pain intensity from baseline.

Time (Hr)	Parecoxib sodium	Diclofenac sodium
0.5	55.23	26.38
1.0	79.1	54.16
4.0	89.55	83.33
8.0	92.53	80.55

Table 5: Pain at the end of eight hours

Nature of pain	ParecoxibSodium(n=20)	Diclofenac Sodium(n=20)
No pain	15	8
Little	5	10
Some	0	2

Table 6: General adverse events

Type of adverse event	Parecoxib sodium	Diclofenac sodium
Nausea	1	3
Vomiting	2	2
Headache	1	1
Dizziness	Nil	1
Skin rash	Nil	Nil
Hypersensitivity	Nil	Nil

4. Conclusion

In conclusion, the results of the study indicate that selective single dose of COX-2 inhibitor parecoxib sodium 40 mg IV is comparable to single dose of diclofenac sodium 75 mg IM Both the drugs are found to be equally and well tolerable as single dose of postoperative analgesic. Additional studies involving larger number of patients will be needed to clearly validate the safety of selective COX-2 inhibitor parecoxib with regard to platelet, renal, and gastrointestinal effects.The question, are thromboembolic risks increased with all COX-2 inhibitors? is legitimate and without a simple answer. It appears that the interplay of multiple factors may confer a higher risk for patient receiving COX-2 inhibitors, yet the risks are unequal across agents. Definitive answers surrounding the safety of COX-2 inhibitors will be derived only by conducting adequately powered, randomized, placebo-controlled, double-blind studies using these agents.

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