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Effectiveness of Oral Diclofenac as Pre-emptive Analgesic

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ABSTRACT
Background:*The pain following major surgery results in delay in the recovery of patients after operation, longer hospitalization period, excess use of analgesics,which is unacceptable. One of the methods for controlling postoperative pain is preemptive analgesia. Preemptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery and in the early postoperative period. Opioids, non-steroidal anti-inflammatory drugs (NSAID) are frequently used for this purpose. Diclofenac sodium is a common, available and cheap NSAIDS.* ***Objectives:*** *The aim of the study was to evaluate the effectiveness of oral diclofenac as pre-emptive analgesic.****Methods:*** *This randomized controlledtrial study was carried out in the Department ofAnaesthesiology& ICU Bangladesh Medical CollegeHospital Dhaka, Bangladesh during 18th January 2020 to 17th July 2020. A total of 100 patients were participated in the study. Sample was selected by random sampling in two groups distributed as- group A (Oral diclofenac sodium), group B (Oral paracetamol). Statistical analyses of the results were obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).****Results:****It was found that majority of the patients i.e. 63.0% were between 40-59 years, mean age was found to 48.3±11.2 years. It was observed that almost two third of thepatientshadASAgrade1ingroupA (58%)andgroupB (56%)respectively.Thedifferencewas not statistically significant (p>0.05) between two groups. At baseline no significant difference of heart rate, SBP, DBP alteration was detected in between groups. Postoperative heart rate and other haemodynamic status were evaluated at 2-hour, 6-hour, 12-hours after surgery.* ***Conclusion:****The postoperative pain management has always been a part of the anaesthesiologist'sroleinthemostimmediatepostoperativeperiod.Present study shows that Oral diclofenac sodium is an effective agent for alleviation of post-operative pain and Opioids requirementinthisstudy,postoperativevisualanaloguescoreswassignificantlylowerin Oral diclofenac sodiumgroup.*

Keywords:*Preemptive analgesia, Diclofenac sodium, Non-steroidal anti-inflammatory drugs (NSAID).*

I. INTRODUCTION

Pain from surgical procedures occurs as a consequence of tissue trauma and may result in physical, cognitive, and emotional discomfort. Almost a century ago, researchers first described a possible relationship between intraoperative tissue damage and an intensification of acute pain and long-term postoperative pain, now referredtoascentralsensitization.Nociceptoractivationismediatedbychemicalsthat are released in response to cellular or tissue damage. Pre-emptive analgesia is an important concept in understanding treatment strategies for postoperative analgesia. Pre-emptive analgesia focuses on postoperative pain control and the prevention of centralsensitizationandchronicneuropathicpainbyprovidinganalgesiaadministered preoperativelybutnotaftersurgicalincision. [1]Thereliefofpainhasalwaysbeenapart of the anaesthesiologist's role in the most immediate postoperative period and the development of acute postoperative pain services has extended this interest beyond the post-anaesthesia care unit. The goal of postoperative pain relief is to achieve optimal analgesia, facilitating a quick return to normal physiologicalfunction.

Preemptive analgesia, an evolving clinical concept, involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the goal of preventing sensitization of the nervous system to subsequent stimuli that could amplify pain. [2] Preemptive analgesia is an antinociceptive treatment that prevents establishment of altered processing of afferent input. The concept was propounded in the early 1980s when experimental studies showed that measures to antagonize the nociceptive signals before injury prevented central hypersensitization, thereby reducing the intensity of pain following the injury. [3]

Clinicalstudieshaveconflictingresultsregardingtheefficacyofpreemptiveanalgesia. [4] Potentialreasonsfortheinability to clinically establish the efficacy of preemptive analgesia include differences in analgesic methods, the complex and multifactorial nature of pain, and the ethical constraints when studying pain inpatients.

Majorabdominalsurgery,whichinducescentralsensitization,hasanincisionalandan inflammatory phase, the latter being a reaction to damaged tissue. Therefore, it has been suggested that antinociceptive protection provided by pre-emptive treatment should extend well into the postoperative period to cover the inflammatory phase in order to be effective. Some animal studies had demonstrated that anesthetic techniques which profoundly reduce the amount of pain information getting into the spinal cord and brain can prevent central sensitization and reduce subsequent pain- related behavior when administered prior to the painful stimulus. [5]However, other animalstudiesdidnotshowthesameresults.Severalpre-emptiveanalgesicregimens have been tried in humans. These include intravenous doses of opioidsnonsteroidal anti-inflammatory drugs, peripheral nerve blocks and multimodal combinations.Treatmentwithnonsteroidalanti-inflammatorydrugsgivensystemically and NMDA receptor antagonists has also been triedpre-emptively. [6]

II. METHODOLOGY

This randomized controlledtrial study was carried out in the Department ofAnaesthesiology& ICU Bangladesh Medical CollegeHospital Dhaka, Bangladesh during 18th January 2020 to 17th July 2020. A total of 100 patients were participated in the study. Sample was selected by random sampling in two groups distributed as- group A (Oral diclofenac sodium), group B (Oral paracetamol). A detailed pre-anaesthetic evaluation including history, thorough clinical examination and all relevant investigations were done for all the patients. All patients instructed preoperatively for the pain visual analogue scale (VAS) for measurement of pain. Tab pantoprazole (20 mg) was given in the night before surgery and in the morning on the day of surgery. The patient in the first group (group A) wasgivenTab.Diclofenac-sodium (50)mgtwohourbeforesurgery andthesecondgroup (group B) was given Oral paracetamol (500mg) 2 h before surgery. A change of BP, pulse, pain status and any complication were evaluated and compared. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).Patients undergoing abdominal operation under general anaesthesia with American society of Anaesthesiogist (ASA)physical status I,II along the with normal renal,hepaticfunction,no allergic history or chronic disease to included in the study.Patient with ASA III, IV, hypersensitivity to test drug, patients with chronic pain , patients with cardiovascular, psychiatric diseases, patients using psychotropic drugs, pregnant patients, geriatric patients, patients with alcohol abuse,patients with abnormal liver function in excluded from the study.Tablet.Diclofenac sodium 50 mg was given to Group A patients and Tablet Paracetamol 500mg given to Group B patients 2hour before surgery.First dose of inj.Tramadol 50mg given intravenous route slowly when patient complained of pain in both group A and group B.

III. RESULTS

Table-1: Age distribution of the study population

Age (years)	Group-A n(%)	Group-B n(%)	P value
20-39	12(24.0)	10(20.0)	0.685^{ns}
40-59	31(62.0)	32(64.0)	
≥60	7(14.0)	8(16.0)	
Mean ±SD	48.3±11.2		

ns= not significant, P value reached from chi square test

Table-1 shows age distribution of the study population, it was observed that the majority of the patients i.e. 63.0% were between 40-59 years, 22.0% of patients were age 20-39 years. Mean age was found to 48.3±11.2 years. The difference was not statistically significant (p>0.05) between two groups.

Table-2: Distribution of study subjects according to BMI (n=100)

Body mass index (kg/m^2)	Group A n(%)		Group B n(%)		P value
	n	%	n	%	
23.1-25.0	19	38.0	22	44.0	0.101^{ns}
25.1-30.0	19	38.0	20	40.0	
>30.0	12	24.0	8	16.0	
Total	50	100.0	50	100.0	

Inthisserieswefoundthatbodymassindex(kg/m^2)wasalmostsimilarinbothgroups, the difference was not statistically significant (p>0.05) between two groups. Maximum patients (44.0%) had observed normalweight.

Table- 3: Distribution of the study patients according to types of ASA status (n=100)

ASA status	Group A n(%)		Group B n(%)		P value
	n	%	n	%	
I	29	58.0	28	56.0	0.790^{ns}
II	21	42.0	22	44.0	

Table shows ASA status of the study patients, it was observed that almost two third (58.0% & 56.0%) patients had ASA grade I in group A and group B respectively. The difference was not statistically significant (p>0.05) between two groups.

Table- 4: Evaluation of heart rate amongst the study subjects (n=100)

Heartrate(beat/min)	Group A n(%)	Group B n(%)	P value
	Mean±SD	Mean±SD	
Baseline	86.7±9.4	85.9±7.1	0.258^{ns}
Range (min-max)	80-110	81-105	
2 hr after	87.7±11.2	92.0±11.9	0.074^{ns}
Range (min-max)	75-110	85-110	
6 hr after	90.7±8.2	98.5±7.7	0.001^{s}
Range (min-max)	80-105	90-110	
12 hr after	94.2±7.8	96.9±7.4	0.206^{ns}
Range (min-max)	80-110	86-110	

At baseline no significant difference of heart rate alteration was detected in between groups; mean heart rate was found 86.7±9.4 beat/min in group A and 85.9±7.1 beat/min in group B. Postoperative heart rate and other haemodynamic status were evaluated at 2h, 6h, 12h after surgery. Present study shows that, at 2 hr after mean heart rate was 87.7±11.2 beat/min and 92.0±11.9 beat/min in group A and group B respectively. At 6 hr after, mean heart rate was 90.7±8.2 beat/min in group A and 98.5±7.7 beat/min in group B. At 12 hr after surgery, mean heart rate was 94.2±7.8 beat/min and 96.9±7.4 beat/min in group A and group B respectively. At after 6 hr difference was statistically significant (p<0.05) between two groups.

Table- 5: Evaluation of systolic blood pressure (SBP) amongst the study subjects (n=100)

SystolicBP(mmHg)	Group A n(%)	Group B n(%)	P value
	Mean±SD	Mean±SD	
Baseline	108.3±5.8	109.6±6.3	1.246^{ns}
Range (min-max)	100-125	100-125	

2 hr after	102.3±4.8	113.6±11.2	0.001[s]
Range (min-max)	100-125	100-125	
6 hr after	107.4±6.2	109.5±6.8	0.083[ns]
Range (min-max)	100-125	100-125	
12 hr after	108.2±5.1	109.6±5.6	0.467[ns]
Range (min-max)	100-125	100-125	

Tableshowssystolicbloodpressureduringfollowupitwasobservedthatatbaseline, mean systolic BP was found 108.3±5.8 mmHg in group A and 109.6±6.3 mmHg in group B. 2 hr after surgery blood pressure was more stabilize in group-A than group-B; mean systolic blood pressure was 102.3±4.8 mmHg and 113.6±11.2 mmHg in group A and group B respectively. At 6 hr after, mean systolic blood pressure was 107.4±6.2 mmHg in group A and 109.5±6.8 mmHg in group B. At 12hrafter,meansystolicbloodpressurewas108.2±5.1mmHgand109.6±5.6mmHg in group A and group B respectively. At 6 hr and 12 hr after surgery difference was statistically non-significant (p>0.05) between twogroups.

Table- 6: Evaluation of diastolic blood pressure (DBP) amongst the study subjects (n=100)

DiastolicBP(mmHg)	Group A n(%) Mean±SD	Group B n(%) Mean±SD	P value
Baseline	60.7±7.4	58.6±6.5	0.856[ns]
Range (min-max)	60-80	60-80	
2 hr after	64.5±8.2	65.4±5.6	1.023[ns]
Range (min-max)	55-80	50-75	
6 hr after	62.1±6.5	64.3±5.9	0.895[ns]
Range (min-max)	50-75	50-75	
12 hr after	61.5±7.3	63.5±7.1	0.901[ns]
Range (min-max)	60-80	60-80	

Regarding diastolic blood pressure during follow up, after 2 hr, mean diastolic blood pressure was found 64.5±8.2 mmHg in group A and 65.4±5.6 mmHg in group B. After 6 hr, mean diastolic blood pressure was 62.1±6.5 mmHg in group A and 64.3±5.9 mmHg in group B. After 12 hr, mean diastolic blood pressure was 61.5±7.3 mmHg in group A and 63.5±7.1 mmHg in group B.

Table- 7: Assessment of pain sensation using Visual Analogue Score (VAS) (n=100)

DiastolicBP(mmHg)	Group A n(%)		Group B n(%)		P value
	n	%	n	%	
2 hr After surgery					
0-2	10	16.6	4	3.3	
3-6	26	53.3	24	46.7	
7-10	14	30.0	22	50.0	
Mean±SD	5.2±0.47		7.4±0.68		0.001[s]
6 hr After surgery					
0-2	27	54.0	13	26.0	
3-6	20	40.0	25	50.0	
7-10	3	6.0	12	24.0	
Mean±SD	31±0.32		5.2±0.51		0.001[s]
12 hr After surgery					
0-2	34	68.0	29	58.0	
3-6	16	32.0	21	42.0	
7-10	0	0	0	0	
Mean±SD	2.1±0.23		2.8±0.27		0.091[s]

The day before surgery patients were instructed about the Visual Analog Scale (VAS) in which 0=no pain and 10=worst pain imaginable. Patients in the group-B had higher VAS, during the second hours (P = 0.0001), compared with the group-A. Mean verbal pain score was 5.2±0.47 and 7.4±0.68 in group A & group B respectively. Sixhoursafterthesurgery,bothgroupsshowed downward trends of the pain VAS, but significantly in group A. Mean score was 3.1±0.32 and 5.2±0.51 in group A & group B respectively. So overall finding suggested that, premptive use of oral Diclofenac sodium reduced the postoperative painsignificantly.

Table-8:DistributionofthestudypatientsaccordingtoAnalgesicrequirement (n=100)

Post-operative analgesic requirement	Group A n(%) Mean±SD	Group B n(%) Mean±SD	P value
Time of 1st demand of analgesic (min)	229.7±24.2	103.8±39.2	0.0001[s]
Total analgesic requirement in 24 hrs(mg)	68.6±8.3	112.5±12.8	0.0001[s]

Table shows the Distribution of the study patients according to post-operative analgesic requirement. Post operatively1st demand of analgesia was earlier in Group-B.Thedifferencewasstatisticallysignificant(p=<0.0001).Totalanalgesicrequirement was higher in Group-B, which was statistically significant (p=<0.0001).

Table- 9: Evaluation of any adverse events (n=100)

Complication	Number of Patient Group A n(%)	Group B n(%)	P value
Hypersensitivity or rash	0	0	0.402
Hypotension	2	0	
Nausea, vomiting	7	4	
Cardiovascular collapse	0	0	
Myoclonus	0	0	

Nausea and vomiting were lower for the group-B, compared with the groups-A; however, this difference was not statistically significant (P = 0.402). In both groups, nauseaandvomitingscoresdecreasedafterthe6thhour,reachingevenzeroafter12 hours.

IV. DISCUSSION

The use of non-opioid analgesics for post- operative analgesia is a standard practice worldwide as it reduces the opioid induced side effects. The combination of two non-opioid analgesics may produce an increased benefit if an additive effect is achieved. We conducted this study to compare the effectiveness of these preparations as postoperative analgesics. To the best of our knowledge, this is the first study which has compared the use of paracetamol and diclofenac at our setting together.

In this study day before surgery patients were instructed about the Visual Analog Scale (VAS) in which 0=no pain and 10=worst pain imaginable. Patients in the group-B had higher VAS, during the second hours (P = 0.0001), compared with the group-A. Mean verbal pain score was 5.2±0.47 and 7.4±0.68 in group A & group B respectively. The difference was statistically significant. Six hours after the surgery, both groups showed downward trends of the pain VAS, but significantly in group A. Mean score was 3.1±0.32 and 5.2±0.51 in group A & group B respectively. At the 12th hour, almost all patients had no pain. So overall finding suggested that, premptive use of oral Diclofenac sodium reduced the postoperative pain significantly. Post operatively1st demand of analgesia was earlier in Group-B. The difference was statistically significant (p=< 0.0001). Total analgesic requirement was higher in Group-B, which was statistically significant (p=< 0.0001).

Similar study was done among four groups. Paracetamol (group one), diclofenac (group two), combination of paracetamol and diclofenac (group three) and placebo (group fore) were given 1 hour before surgery. The rescue analgesia was provided with morphine postoperatively in the first 24 hours of postoperative period. Intensity of pain, time and dose to first rescue analgesia and total analgesic requirement were recorded.

Dose of first rescue analgesic, mean VAS, mean morphine and total morphine requirements were lowest in combination group. Time to first rescue analgesic was prolonged in diclofenac and combination group as compared with paracetamol and placebo. Global satisfaction score as regard to postoperative pain at 12 hours and 24 hours were significantly better in combination and diclofenac group as compared to paracetamol and placebo. So, diclofenac possesses better pre-emptive analgesic efficacy than paracetamol.

The mechanism of action of diclofenac goes beyond COX inhibition and includes inhibition of thromboxane-prostanoid receptor, affecting arachidonic acid release and uptake, inhibition of lipoxygenase enzymes and activation of the nitric oxide‐ cyclic guanosine monophosphate anti-nociceptive pathway. Whereas, action of paracetamol is due to inhibition of COX‐ 2‐ dependent pathways that are proceeding at low rates. The analgesic effect of paracetamol is central and is due to activation of descending serotonergic pathways, but its primary action may be inhibition of PG synthesis.

Tuzuner et al, studied the effect of 1 g intravenous paracetamol, 75 mg intramascular diclofenac and 8 mg intravenous lornoxicam in 60 patients undergoing surgical removal of third molar and found the pain scores to be comparable in all the groups. [7]In our study, in patients undergoing abdominal surgery, we found that Diclofenac sodium appears to be a superior post-operative analgesic compared to paracetamol, in terms of rescue analgesic requirements.

Diclofenac sodium may be a better analgesic option if no relative or absolute contraindications to its use exist and paracetamol may be considered in patients where its relative safety profile is of importance. Combination is not favored as it may increase side effects and cost and with no additional benefit. However further research works with larger sample size are suggested to draw definitive conclusions and influence formulation of post‐ operative pain management strategy. [8]

Limitations of the study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

V. CONCLUSION

Result of the present study, suggested that preemptive oral Diclofenac sodium had significant effect on reducing postoperative pain and postoperative analgesic requirement in patients planned for abdominal surgery. Surgical pain results from traction of tissues during surgery, surgical wound and surgical drains. The intensity of pain is greatest during the first postoperative day and requires efficient pain control. Different analgesic drugs have been used for this purpose and combination of opioid and non-opioid analgesic drugs has shown a quality of postoperative pain control. Excessive use of opioids may result in side effects like respiratory depression, but preemptive use of Diclofenac sodium has shown to decrease the total dose of Tramadolrequiredinsurgicalpatientsandthuslowersthechanceforsideeffects.The null hypothesis of this study was that there should be no difference in preemptive analgesic effect of Diclofenac sodium and paracetamol in reducing opioid requirements in patients undergoing abdominal surgery. The results were in contrary to our null hypothesis and showed that a single dose of 50 mg of Diclofenac sodium given before surgery significantly reduces the postoperative opioids requirements during the first 24 hours. But haemodynamic parameters (HR, SBP, DBP) almost similar in bothgroups.

VI. RECOMMENDATION

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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