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AN EVALUATION OF PRE-EMPTIVE ANALGESIA IN PATIENTS UNDERGOING MINOR SURGICAL PROCEDURES BY ADMINISTERING PENTAZOCINE, FENTANYL AND TRAMADOL AS PRE-OPERATIVE ANALGESICS AND KETOROLAC AS POST-OPERATIVE ANALGESIC – A COMPARISON USING KETOROLAC AS STANDARD DRUG.

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ABSTRACT

Objectives: To assess role of Preoperative analgesia in short surgical procedures and comparing the effectiveness of three commonly used analgesic drugs such as pentazocine, fentanyl, ketorolac and tramadol in post-operative pain relief when used as preoperative analgesics in short surgical procedure. **Methods:** The 15 patients had been divided into four groups. Three groups received medication preoperatively and the fourth group was the control group. Post-operative analgesic was given on patients demand. The duration of pain relief had been taken from inception of relief till the time it lasts. In Control Group postoperative analgesic 30 mg IM Ketorolac had been given on demand. **Results:** Group I received tramadol, Group II received pentazocine while Group III received fentanyl. From these patients 25 cases were male and 35 cases were female, male female ratio was 1:1.4. So, distribution was almost symmetrical. Pain score and Sedation score was recorded at different interval. **Conclusions:** The postoperative analgesic management should be a continuance of the multimodal analgesia

provided before surgery. Communication between the anesthesiologist and general surgeon and even dental surgeon is important to achieve a protocol with the best short- and long-term outcomes for the benefit of the patient.

KEYWORDS: Sedation, pre-operative analgesics, Post –operative analgesics.

INTRODUCTION

Pain is defined by Marskey et al. as "unpleasant sensory and emotional experience associated with actual or potential tissue damage".[1] Pain is transmitted through numerous inflammatory mediators released in response to tissue injury. Post-operative pain is an acute phenomenon which begins with surgical trauma and usually ends with tissue healing. The problem of inadequate post-operative pain relief has been recognized for many years and has been the subject of considerable research. A recent concept for the relief of post-operative pain has been production of preoperative analgesia. Most of the patients complain pain after short surgical procedure and a patient with adequate post-operative analgesia has a lessened incidence of pulmonary, cardiovascular, thrombo-embolic and other complications due to better free mobility. Physiological and behavioral studies of animal have demonstrated that noxious stimulus induced pain can be prevented or reduced by the administration of analgesic agent prior to surgery. Classically three classes of drugs have been used prior to surgery: Local Anaesthetics, Opioids and NSAIDs either alone or in combination.[1]

The term "pre-operative analgesia" implies that analgesia given before the painful stimulus which prevents or reduces subsequent pain. The concept that preoperative analgesia might be worthwhile originates from basic science studies.

Peripheral tissue injury provokes two kinds of modification in the responsiveness of the nervous system: peripheral sensitization, a decline in the threshold of nociceptor afferent peripheral terminals and central sensitization. these changes contribute to the post injury pain hypersensitivity state found postoperatively, which manifests as an increase in the response to noxious stimuli and a decrease in the pain threshold, both at the site of injury and in the surrounding uninjured tissue.[2] There is both scientific and clinical interest in this effect. The scientific interest is in the mechanism underlying the effect; the clinical interest is in the potential for improving postoperative pain management.[3] Minimizing pain is in keeping with the physician's primary goal of relieving suffering. Moreover, effective treatment of preoperative and postoperative pain also represents an important component of postoperative

recovery as it serves to blunt autonomic, somatic, and endocrine reflexes with a resultant potential for decrease in preoperative morbidity. Noxious stimuli, such as surgical trauma and subsequent postoperative pain, result in a broad range of endocrinological, immunological, and inflammatory responses, including increased release of catabolic hormones and inhibited secretion of anabolic mediators. This group of responses is known collectively as the neuroendocrine stress response to injury. The stress response results in catabolism, arrhythmogenesis, hypercoagulability, and immunosuppression. Pain causes reflex activation of cardiac sympathetic fibers with increases cardiac work and an associated increase in myocardial oxygen demand. These changes may be maladaptive after an operation. Minimizing the afferent drive and accordingly the stress response may enhance recovery. [4] The provision of adequate postoperative analgesia alone does not guarantee an amelioration of the stress response. The systemic administration of opioids has only a modest effect in this regard, even though it can provide excellent postoperative analgesia.

The aim of this study is to know validity of Preoperative analgesia as a routine treatment strategy in short surgical procedures and comparing the effectiveness of three commonly used analgesic drugs.

The pros and cons of this form of therapy also taken into consideration, the risk of complications, the measures necessary to monitor the patients and administering the treatment if any complication develops, as well as setting up protocol to relieve post-operative pain of short surgical procedures.

MATERIALS AND METHODS

The study had been conducted in the department of Surgery, Orthopedics, anesthesia & Obs. & Gyn. at our institute. This study was performed in 60 patients' undergone different types of elective short surgical procedure under local Anesthesia.

The patients had been divided randomly into four groups of 15 patients in each group. Three groups received medication preoperatively and the fourth group was the control group in this group post-operative analgesic was given on patients demand. The duration of pain relief had been taken from inception of relief till the time it lasts.

Control Group- In this group postoperative analgesic 30 mg IM Ketorolac had been given on demand.

Group I-These patients received intravenous tramadol 50 mg, 15 minutes before surgery as preoperative analgesic.

Group II-These patients received intravenous Pentazocine 30 mg, 15 minutes before surgery as preoperative analgesic.

Group III-These patients received intravenous Fentanyl 50 µg, 15 minutes before surgery as preoperative analgesic.

Visual analogue scale with 0 and 10 labeled as "no pain" and "worst imaginable pain" respectively was explained to the educated patients visit. Post-operative analgesia in all groups had been given with I.M. ketorolac 30 mg given on demand. Post-operatively grading of pain was done half hourly for one hour then 2 hourly for 6 hours. Any side effect like nausea, vomiting, pruritus was also noted. After through assessment of the effect of drug in each group on the basis of above mentioned parameters tabulation was done and each group was compared with the control group to work out the significance of scores noted down and there by acceptability of drugs with their relative merits and demerits. Statistical calculations were done to evaluate the different readings.

RESULTS

The statistical comparison was done by simple't' test. The't' value was obtained at 28 *d.f.* The 'p' value was obtained by't' test chart at 28 *d.f* which shows that if the't' value was <2.05 then 'p' was greater than 0.05 and this was insignificant. If value was >2.05 then p was <0.05 and this was significant. For't' value >2.76 the p value was <0.01 and it was highly significant. For't' value >3.67 then 'p' was 0.001 and this was most highly significant. Statistical comparison was done between I, II, III and IV groups.

Table 1: showing sex distribution and total number of cases in each group.

Groups	Male		Female		Total	
	NO.	%	NO.	%	NO.	%
Control Group	8	53.33	7	46.67	15	25
Group 1	7	46.67	8	53.33	15	25
Group 2	4	26.67	11	73.33	15	25
Group 3	6	40	9	60	15	25
Total	25	41.66	35	58.33	60	100

Table 2: showing different type of surgical procedures done in each group.

Operations	Control Group		Group 1		Group 2		Group 3		Total	%
	no	%	no	%	no	%	no	%		
D& C	2	13.3	5	33.3	3	20	1	6.66	11	18.3
Abscess	1	6.66	4	26.6	2	13.3	6	40	13	21.6
Suturing	2	13.3	2	13.3	2	13.3	2	13.3	8	13.3
Lipoma Excision	1	6.66	1	6.66	1	6.66	1	6.66	4	6.66
Cyst Removal	3	20	2	13.3	4	26.6	2	13.3	11	18.3
Dislocation	2	13.3	-	-	1	6.66	-	-	3	5
Debridement	2	13.3	1	6.66	-	-	-	-	3	5
Marsupilization	1	6.66	-	-	1	6.66	2	13.3	4	6.66
Cervical Biopsy	1	6.66	-	-	-	-	-	-	1	1.66
Endometrial Biopsy	-	-	-	-	1	6.66	-	-	1	1.66
Hydrocoeal	-	-	-	-	-	-	1	6.66	1	1.66

Table 3: showing pain intensity score at different intervals in different groups postoperatively.

Group	No. Of Patients Falling In Grading Of Pain at																			
	Immediate postoperative				At 30 mins postoperative				At 2 hrs postoperative				At 4 hrs postoperative				At 6 hrs postoperative			
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Control n=15	0	3	12	0	8	4	3	0	5	6	4	0	4	3	8	0	5	4	6	0
Group 1 n=15	11	2	2	0	4	6	5	0	6	5	4	0	5	6	4	0	8	5	2	0
Group 2 n=15	11	1	3	0	10	2	3	0	12	1	2	0	4	6	5	0	8	4	3	0
Group 3 n=15	12	3	0	0	10	5	0	0	9	6	0	0	2	5	8	0	2	6	7	0

Table 4: showing number of patients demanding rescue analgesics at different intervals in different groups.

Groups	Immediate Postoperative	At 30 mins postoperative	At 2 hrs post operative	At 4 hrs postoperative	At 6 hrs postoperative
Control	n=12	n=3+12	n=0	n=0	n=0
Group 1	n=2	n=5+2	n=4+7	n=4+11	n=0
Group 2	n=2	n=3+2	n=2+5	n=5+7	n=3+12
Group 3	n=0	n=0	n=0	n=8	n=7+8

Table 5 showing side effects in different groups

Side effects	Control		Group 1		Group 2		Group 3		Total	
	No	%	No	%	No	%	No	%	No	%
Nausea	1	6.66	-	-	-	-	1	6.66	2	3.33
Vomiting	1	6.66	-	-	-	-	2	13.33	3	5
Bradycardia	-	-	-	-	-	-	1	-	3	-
Hypotension	-	-	-	-	-	-	-	-	2	-
Shivering	-	-	-	-	-	-	-	-	1	-
Pruritus	-	-	2	13.333	-	-	-	6.66	1	5
Urinary retention	-	-	1	6.66	-	-	-	6.66	-	3.33
Respiratory	-	-	-	-	1	6.66	1	-	1	1.66

Table 6: showing sedation score at different intervals.

Groups	Immediate post-operative			1 hour Post-operative			3 hours Post-operative			6 hours Post-operative		
	Mean SD ±	t	P	Mean SD ±	t	P	Mean SD ±	t	P	Mean SD ±	t	P
Control	0.33±0.48	-	-	0.60 ± 063	-	-	0±0	-		0±0	-	-
Group 1	0.53±0.966	0.94	INS>0.0	0.353 ± 0.48	1.27	INS>0.05	0±0	-		0±0		
Group 2	0.86 ±0.274	2.24	SIG>0.0	0.26 ±0.45	1.39	INS>0.05	0±0	-		0±0		
Group 3	1.33 ± 0.6	4.8	MHS>0.001	0.66 ±0.72	0.23	INS>0.05	0±0	-		0±0		

Table 7: showing vas score at different intervals with statistical evaluation.

Groups	Immediate post-operative			1 hour Post-operative			3 hours Post-operative			6 hours Post-operative		
	MEAN SD ±	t	P	MEAN SD ±	t	P	MEAN SD ±	t	P	MEAN SD ±	t	P
Control	4.2±1.14	-	-	1.06 ±2.02	-	-	2.66±1.87	-	-	2.46+2.09	-	-
Group 1	1.06±2.01	5.08	<0.001	2.6 ± 2.2	1.29	>0.05	2.06±1.83	0.85	>0.05	1.46+1.99	1.29	>0.05
Group 2	1.13±1.99	5.00	<0.001	1.66 ±2.2	0.07	>0.05	2.33±2.05	0.44	>0.05	1.53+2.06	1.18	>0.05
Group 3	0.46±0.99	9.26	<0.001	0.93±1.3	1.02	>0.05	3±1.92	0.47	>0.05	3.0+2.03	0.69	>0.05

Table 8: showing side effects in different groups.

Side effects	Control		Group 1		Group 2		Group 3		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Nausea	1	6.66	-	-	-	-	1	6.66	2	3.33
Vomiting	1	6.66	-				2	13.33	3	5
Bradycardia	-	-	-	-			1	-	3	-
Hypotension	-	-	-	-			-	-	2	-
Shivering	-	-	-	--	-	-	-	-	1	-
Pruritus		-	2	13.33	-	-	-	6.66	1	5
Urine retention		-	1	6.66	-	-	-	6.66	-	3.33
Respiratory		-	-	-	1	6.66	1	-	1	1.66

DISCUSSION

This study entitled "A comparative study of pentazocine, fentanyl, ketorolac and tramadol in patients undergoing short surgical procedures used as pre-operative analgesics" was done in 60 patients to establish the role of pentazocine, fentanyl, tramadol and ketorolac in post-operative pain relief.

The patients had been divided randomly into four groups of 15 patients in each group. Three groups had been received medication preoperatively and fourth group was the control group in this group post-operative analgesic given on patients demand. Out of 60 patients studied, 25 cases were male and 35 cases were female, male female ratio was 1:1.4 (table 1). So distribution was almost symmetrical.

In this study youngest patient was of 18 years of age and the oldest patient was 60 years. Maximum cases were between 25 to 45 years of age In this study, dilatation & curettage, abscess drainage, suturing and cyst removal were the most common procedure done and constituted 18.33%, 21.66%, 13.33%, 18.33% of total cases respectively (table2). Statistical evaluation and comparison of every group had been done with control group using student ‘t’ test.

Table No. (3) & (4) shows pain score at different interval in different groups and statistical evaluation of mean pain score compared with control group. In control group all the patients received rescue analgesic immediately or within 30 minutes. In group I and group II most of patients were comfortable up to 2 hours post-operatively. On statistical evaluation mean pain score was found to be most highly significant t =4.06 ($p<0.00l$) at immediate post-operative in group I, and insignificant at different intervals. In group II mean pain score was most highly significant t value=4.82 ($p<0.001$) at immediate post-operative and significant t = 2.10 ($p<0.05$) at 2 hours post-operative. In group III almost all patients were comfortable and did not complain of pain upto 2 hours .operative. On statistical evaluation mean pain score was most highly significant t = 5.88 ($p<0.001$) at immediate post-operative, and was insignificant at all other intervals.

Pain score was found to be highly significant in immediate postoperative and up to l hour in all the groups.

Table No. (5) Shows number of patients demanding rescue analgesics at different intervals. In the control group relatively a high number of patients required rescue analgesic and had been given analgesic within 30 minutes of postoperative period. In group I and group II very few number of patients required rescue analgesic immediate postoperatively. At 30 minutes the number in group I increased to five from previous two and four at 2 hours postoperatively and remainder at 4 hours post-operatively.

In group II the number of patients requiring rescue analgesic was found to be three at 30 minutes two at 2 hours post-operatively five at 4 hours postoperatively and three at 6 hours post-operatively.

In group III no patients required rescue analgesics till 2 hours and about 50% of patients demanded rescue analgesia at 4 hours post-operatively the remaining required rescue analgesics at 6 hours post-operatively.

Table No. (6) shows sedation score at different intervals with statistical evaluation compared with control group and the patients were falling in control group sedation score had been found to be insignificant. Significant sedation was in group II at immediate post-operative, t value = 2.24 ($p<0.05$) in group III sedation score was most highly significant t value = 4.8 ($p<0.001$) at immediate post-operative, and was insignificant at other intervals.

Table No. (7) shows visual analogue score at different intervals with statistical evaluation. VAS was found to be most highly significant in all the groups when compared with control group immediate post-operatively when group I compared with control group found t value = 5.008 ($p<0.001$) at immediate post-operatively. Insignificant was in all the intervals, in group II was, t value = 5.00 ($p<0.001$) at immediate postoperative, and insignificant was all other intervals and in group III was t value = 9.26 ($p<0.001$) at immediate post-operative, and was quite insignificant at other intervals when compared with control group.

Robert Jan M. et al study was designed to investigate the efficacy of intravenous tramadol and morphine for moderate to severe Post-operative pain. It was shown that whereas the analgesic potency of tramadol and morphine are similar, the respiratory depression with Tramadol was clinically irrelevant.[26] Margini et al conducted a controlled, completely randomized trial which was designed to compare the efficacy and safety of tramadol and pentazocine in the treatment of post-operative pain. A total of 50 patients undergoing

hemorrhoidectomy or traumatological or abdominal surgery following a randomized list, each patient was given 100 mg of tramadol and 30mg pentazocine by I.M. route at 8 hours interval for 3 days. Efficacy was assessed by VAS. They concluded that the first dose of tramadol was significantly more effective than pentazocine after the Ist hour and throughout the subsequent 5 hours. Final judgments on efficacy and acceptability were in favor of tramadol.[37] Milligan K. et al studied on 60 patients to compare the effect of intramuscular diclofenac, ketorolac, or piroxicam on post-operative pain following laparoscopy.

All patients were free from systemic illness and concurrent non-steroidal medication. Pre-operatively a visual analogue scale of 0-10 was explained to the patient, following a standard anaesthetic technique of propofol 2 mg/kg. Fentanyl 1 mcg/kg, Atracurium 0.3mg/kg and maintenance with 1-1.5% Isoflurane in 60% nitrous oxide. Patients were randomly allocated to diclofenac, ketorolac, piroxicam groups, receiving intramuscular injection diclofenac 75 mg, ketorolac 30 mg or piroxicam 20 mg respectively. And post-operative recovery is assessed by VAS score on admission to recovery ward, and they found that piroxicam 20 mg when given as an intramuscular injection compared favorably with ketorolac and diclofenac in respect to VAS score number of patients not requiring further analgesia and time to first analgesia.[24]

Mark Tvershoy et al administer pre-emptive fentanyl 5 ug/kg with standard technique of general anaesthesia to assess the effect on post-operative pain, they found VAS score was 1.69±0.19 ($p<0.001$) in the fentanyl group. The results suggest that fentanyl pre-emptively decreases postoperative wound hyperalgesia. In our study VAS score was 0.46±0.99 (p0.001) it was most highly significant in fentanyl group.[28] Olle fortuny et al **c**ompared the analgesic efficacy of ketorolac and tramadol in post-operative pain. They gave tramadol 100 mg and ketorolac 30 mg each group separately every 6 hours intravenously. They showed that mean VAS score throughout the study was 3.6 for tramadol group and 4.4 for ketorolac group. The VAS score in tramadol group were statistically lower than those of ketorolac group ($p<0.05$). So, they concluded that during first 12 hours following surgery a 100 mg dose of tramadol has been shown to provide more effective pain relief than 30 mg ketorolac administered *i.v.* every 6 hours.[41] T. J. Parke et al administered ketorolac 30 mg intravenously 30 minutes before surgery and saline *i.v.* at the end of surgery in group I. In group II saline had been given 30 minute before surgery and 30 mg ketorolac *i.v.*at the end of surgery. They observed that peri-operative opioid requirement and 24 hours pain score were significantly reduced in

the pre-emptive group ($p<0.05$). So they concluded that preoperative ketorolac reduced perioperative morphine requirement and resting pain score at 24 hours compared with post-operative ketorolac PCA morphine requirement were no significantly different. So this study demonstrated that single dose ketorolac is more efficacious if given pre-operative.[30] Lee VC et al Administered 30 mg ketorolac *i.v.* In study group and *i.v.* saline given as placebo pre-operatively. They observed that the mean initial VAS score was more than double in placebo group (the VAS in study group was 2.3±1.0) and the VAS in placebo group was 5.1±1.0. So they concluded that 30 mg ketorolac given prior to orthoscopic knee surgery decreased post-operative pain as well as requirement of post-operative narcotics.[17] Power et al After cholecystectomy ketorolac 30 mg gave poor analgesia in the immediate post-operative period, when compared with morphine 10 mg but on the next day the effects of two drug were similar. This was demonstrated by observation of pain intensity, pain relief, time taken by next injection and overall assessment of analgesia. The base line pain intensity in the immediate postoperative period was severe and the next day it was moderate.[21] O.Hara et al found the ketorolac 30 mg was at least, as effective as morphine 12 mg in relieving moderate to severe pain after various operation, including major surgery.[45] Gilies GWA et al observed that ketorolac is a poor analgesic in immediate P.O. period; the ketorolac group expressed overall satisfaction with their analgesia and required only small dose of rescue morphine (10 mg) in the first 24 hours. There result may indicate that the quality of ketorolac analgesia become similar to that of morphine after the initial post-operative period.[46] K.L. Tulsiani et al (1997) conducted a study to assess the analgesic efficacy, safety and duration and action of *i.v.* tramadol and pentazocine given intra operative and post-operatively. Pain intensity was graded by the patients' verbal rating score. They observed that tramadol has an overall analgesic profile superior to pentazocine.[47]

Table no. (8) shows side effects in different groups. In the control group, nausea and vomiting was found and no systemic or local side effects were seen. In group I, bradycardia was seen in two patients which was found to be about 13.33%. Hypotension in one and respiratory depression in one patient were noted, i.e. 6.66% for each. In group II shivering was noted in one i.e., 6.66%, pruritus in one i.e. 6.66% and respiratory depression in two patients i.e. 13.33%. In group III**,** the incidence ranging from, nausea, vomiting, bradycardia, hypotension to respiratory depression nausea was found in one i.e. 6.66%, vomiting in two i.e. 13.33%. Bradycardia, hypotension and respiratory depression were noted in 3 patients (one feature in each) i.e. 6.66% for each one. J.E.G. Rogers et al gave 10 mg ketorolac before

induction given 10 mg. Ketorolac in 30 patients before skin incision and a control group of 20 patients did not receive ketorolac, they found the patients control analgesic dose in group of ketorolac given before skin incision was less than that of control group. There were no other statistically significant differences in between the groups. Median blood loss in the group given ketorolac before operation exceeded that of patients who did not receive ketorolac before operation. The incidence of nausea and vomiting was similar in the both groups and incidence of pruritus was not noted in the groups receiving ketorolac before operation.[31]

In our study there was no any complaint of pruritus in group where ketorolac was given after surgery. The incidence of nausea & vomiting was 6.6% both.

Tulsiani K. L. et al (1997) conducted a study to compare the analgesic efficacy, safety and duration of action of intravenous tramadol pentazocine given intraoperatively and post-operatively. They found that tramadol has marked less side effects like nausea, vomiting, drowsiness and respiratory depression.[47] Mamta (1997) concluded that intravenous tramadol was a good alternative narcotic analgesic than the buprenorphine and pentazocine as it offers less respiratory depression, less fear of addiction and sedation and minimal side effects.[35] Lee V.C. et al (1986) gave ketorolac 30 mg prior to arthroscopic knee surgery. They observed that sedation incidence, nausea and vomiting were not significantly different between groups.[17] Olle Fortuny G. et al (2000) studied on 70 patients undergoing abdominal hysterectomy. Two treatment group were formed, tramadol and ketorolac group. They concluded that administering the drug intravenously caused the high incidence of post-operative vomiting.[41]

CONCLUSION

- Pre-operatively intravenous tramadol and pentazocine had been found to have pain scores more than fentanyl; duration of pre-operative analgesia was found to be more in fentanyl group and almost equal in tramadol and pentazocine group.
- No rescue analgesic required up to two hours in group who received fentanyl while most of the patients required analgesic immediate post-operatively in control group but it was required immediate post-operative in few patients in tramadol and pentazocine group.
- Most highly significant sedation score had been found in the fentanyl group and significant sedation score was found in the pentazocine group and lowest sedation score

found in tramadol group. But at 3rd hour sedation score was found almost equal in all groups.

- The VAS score was statistically highly significant in fentanyl group. Pentazocine group and tramadol group come subsequently.
- Nausea and vomiting was frequent with fentanyl group, although it was observed in tramadol group also.
- Keeping in view all the factors considered in this study the administration of analgesic agents given 15 minutes before surgery definitely reduced the analgesic requirement in the post-operative period. Therefore the hypothesis of preoperative analgesic is well established with the result of our study.
- Pre-operative intravenous fentanyl was found to be best analgesic which has shown very good analgesia and sedation along with few side effects. Pre-operative *i.v.* tramadol was found to be next best with good analgesia, poor sedation with minimal side effects and pre-operative *i.v.* pentazocine were on third place with good analgesia, good sedation with minimal side effects. Therefore pre-operative administration of fentanyl 50µg 15 minutes before surgery in patients undergoing short surgical procedures for better control of postoperative pain. As this was single dose study, it needs other studies for further analysis. A firm conclusion regarding the time of intervention (i.e. pre-operatively, postoperatively) for optimal pain control is a point for clarification and needs further analysis.

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