

Effectiveness of acetaminophen in control of breakthrough pain: Randomized controlled trial

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Abstract

Objective: To reduce postoperative pain by using additional analgesic agent in between the usual parenteral analgesia that is used in the postoperative period in surgical patients.

Methods: The double-blind, randomised control intervention was conducted from June to November 2015 at Rehman Medical Institute, Peshawar, Pakistan, and comprised postoperative surgical patients of either gender aged 18 or more who had undergone uneventful elective surgery. The subjects were divided into test and placebo groups. In the test group, 1gm acetaminophen was additionally prescribed, while in the control group placebo (starch) was administered. Demographics were noted and pain score was recorded using three internationally validated pain scales; Verbal pain intensity scale, Visual analogue scale, and Numeric pain scale. SPSS version 15.0 is used for calculation. Data was collected twice over 48 hours.

Results: Out of 220 patients, 165(75 %) were male with mean age 31.5 ± 1.93 years and 55(25%) were female with mean age 31.5 ± 1.48 years. There were 118(53.6%) patients in the test group and 102(43.4%) in the control group. In the first 24 hours the cumulative pain score, from numeric pain scale and visual analogue scale, for the control group showed 5(4.90%) patients had no pain, 39(38.24%) had mild pain, 52(50.98%) moderate pain and 6(5.80%) had severe pain. In the test group, 13(11.02%) reported no pain, 83(70.34%) had mild pain, 19(16%) had moderate pain while 3(2.54%) complained of severe pain. In the next 48 hours cumulative pain score in the test group showed 44(37.29%) subjects had no pain, 67(56.78%) had mild pain, 6(5.08%) had moderate pain, 1(0.85%) had severe pain, while in the control group 10(10%) had no pain, 56(55%) had mild pain, 33(32%) had moderate pain and 3(3%) had severe pain.

Conclusion: Additional acetaminophen reduced mild to moderate pain between two doses of parenteral analgesia.

Keywords: Effectiveness of acetaminophen, Breakthrough pain, Parental analgesics ketorolac trometamine, Post surgical patients. (JPMA 68: 994; 2018)

Introduction

Pain is defined as an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage.¹

The concept of no postoperative pain following surgery was forwarded as a fundamental human right in 2004 by European Federation of International Association for the study of Pain (IASP) and by the World Health Organisation (WHO) as 'Global Day against Pain'.²

Various studies have shown that complete achievement of pain-free state, in pain management setup, is impossible to achieve and they have attributed it to societal, cultural, religious, political attitudes toward pain control and also acceptance of torture.¹ Inadequate training of medical and nursing staff is also considered as a major reason behind poor pain control.²

This study is a sequel to the study conducted at the same

institute in which postoperative pain management in the surgical wards was studied. The result of that study had showed that far too many postoperative patients were suffering from mild (40% in 24 hours and 56% in 48 hours) to moderate (39 % in 24 hours and 33% in 48 hours) pain.³

We hypothesised that the mild to moderate pain in postoperative patients was in fact the breakthrough pain that occurred between the doses of parenteral analgesia that was given to these patients. Break through pain was defined as the discomfort, usually acute and severe, which is experienced by patients between the normal doses of medication that generally controls or palliates such pain.⁴ The current study was planned to see if we could decrease the degree of postoperative pain by using an additional analgesic agent in between the usual parenteral analgesic doses. Due to well-documented pharmacokinetics and pharmacodynamics, acetaminophen was chosen as the interventional drug for this purpose.

Patients and Methods

The double-blind, randomised control intervention was conducted from June to November 2015 at Rehman

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Medical Institute, Peshawar, Pakistan. The study was approved by the institutional ethics review board and consent was taken from surgical consultants who allowed their patients to participate in the study. The sample size was calculated, using WHO formula with confidence Level at 95%.⁵

$$n = \frac{2(Z_{\alpha} + Z_{1-\beta})^2 \cdot \Delta^2}{\Delta^2}$$

The subjects were divided into test and placebo groups. Allowable error (E) was 10% and extra subjects were included in each group to compensate for dropouts and exclusions. Random assignment to the groups, using coin toss to determine allocation, was used. All postoperative surgical adult patients of both genders who had undergone uneventful elective surgery were included in the study except cardiology and gynaecology patients. Patients with altered conscious level, with abnormal liver function tests, and those below 18 years of age were also excluded. Basic characteristics of all the participants were recorded using a proforma. Information included name, age, gender, weight, height and the specialty under which the patient was admitted. In the test group, 1gm acetaminophen was prescribed while in the control group placebo (starch) was administered. Both agents were given 2 hours following the parenteral analgesia ketorolac tromethamine (Figure-1). Pain was then recorded 2 hours later following the interventional drug and placebo tablets, using 3 internationally validated pain scales: Verbal pain intensity scale (VPIS), Visual analogue scale (VAS) and Numeric pain scale (NPS). Data was collected twice in 48 hours. Double blinding was maintained at all stages. Data was then analysed using SPSS. Mean score of all three scales were calculated separately. Cumulative scale of VAS and NPS were also obtained. All variables were analysed for frequency and related calculations. Quantitative variables were analysed for means and standard deviation (SD). Comparison was made between the test and control group for significant differences of frequencies and means using the Chi Square test and student's T-test respectively, keeping $p \leq 0.05$ as significant. Further comparison was also made based on duration of operation. Analysis of variance (ANOVA) test was done to record the difference of pain score and the pain control for the 3 groups or duration of surgery.

Result

Out of 220 patients, 165(75 %) were male and 55(25%)

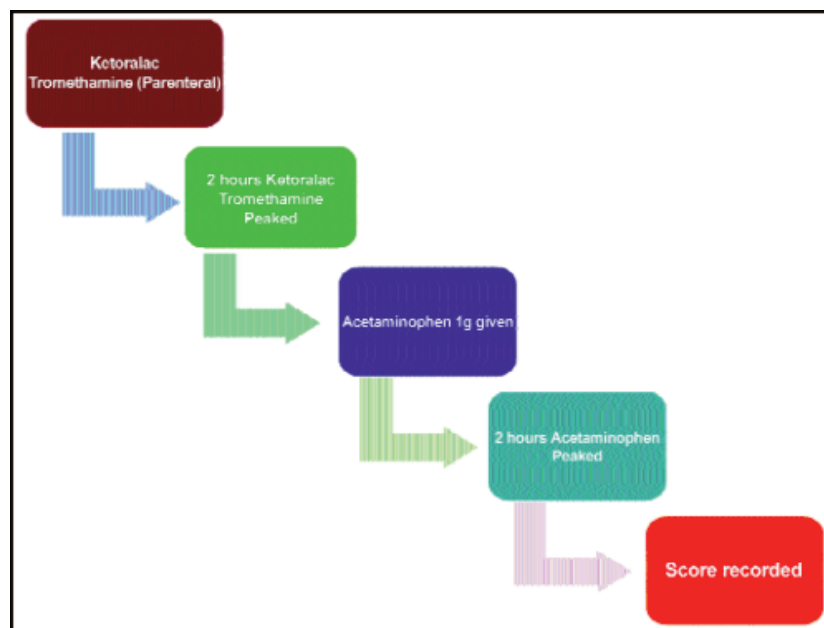


Figure-1: Procedure of administration of acetaminophen.

were female, and 130(59.1%) were below the age of 50 years (Table-1). There were 118(53.6%) patients in the test

Table-1: Demographic data of patients (n=220).

#	Variables	Frequencies	Percentages
1.	Gender		
	Male	165	75
	Female	55	25
2.	Age groups (years)		
	18-29	60	27.3
	30-39	35	15.9
	40-49	35	15.9
	50-59	30	13.6
	60-69	38	17.3
	70-79	10	4.5
	80-89	12	5.5
3.	Duration of surgery (hours)		
	<2	171	77.7
	2-6	42	19.1
	>6	7	3.2
4.	Surgical Specialty		
	General surgery	65	29.5
	Orthopaedics	56	25.5
	ENT	10	4.5
	Urology	62	28.2
	Plastic surgery	3	1.4
	Oral and maxillofacial surgery	5	2.3
	Neurosurgery	19	8.6
5.	Study groups		
	Acetaminophen	118	53.6
	Placebo	102	46.4

ENT: Ear, nose and throat.

Table-2: Frequency distribution of categories of pain scores between test and placebo groups based on pain scales and overall pain score.

#	Pain score	Placebo f (%)	Test group f (%)	Chi square value	Total	P value
1.	VP 24 hours					
	No pain	07 (6.9%)	16 (13.6%)	53.97	23 (10.5%)	<0.001
	Mild pain	21(20.6%)	71 (60.2%)		92 (41.8%)	
	Moderate pain	48 (47.1%)	26 (22.0%)		74 (33.6%)	
	Severe pain	26(25.5%)	05 (4.2%)		31 (14.1%)	
2.	VP 48 hours					
	No pain	33(32.4%)	44 (37.3%)	7.074	77(35.0%)	0.132
	Mild pain	36(35.3%)	51 (43.2%)		87(39.5%)	
	Moderate pain	27(26.5%)	20(16.9%)		47(21.4%)	
	Severe pain	06(05.9%)	03 (2.5%)		09(4.1%)	
3.	VAS 24					
	no pain (0-1)	12(11.8%)	49(41.5%)	50.6	61(27.7%)	<0.001
	Mild pain (2-3)	39 (38.2%)	51(43.2%)		90(41%)	
	Moderate pain (4-6)	44 (43.1%)	15(12.7%)		59(26.8%)	
	Severe pain (7-9)	05 (2.0%)	03(5.5%)		08(3.70%)	
4.	VAS 48					
	No pain =(0-1)	25(24.5%)	79 (66.9%)	48.99	104(47.3%)	<0.001
	Mild pain (2-3)	42 (41.2%)	31 (26.2%)		73(33.4%)	
	Moderate pain (4-6)	30 (29.4%)	07 (5.8%)		37(16.8%)	
	Severe pain (7-9)	04 (3.9%)	01 (0.8%)		05(2.30%)	
5.	NPS 24					
	No pain =0	08(7.8%)	22 (18.6%)	46.96	30 (13.6%)	<0.001
	Mild pain (1-3)	42(41.1%)	77 (65.2%)		119(54.1%)	
	Moderate pain (4-6)	45(44.1%)	18 (15.3%)		63(28.6%)	
	Severe pain (7-9)	07(6.8%)	10 (0.8%)		08(3.6%)	
6.	NPS 48					
	No pain=0	16 (15.7%)	58(49.2%)	55.32	74(33.6%)	<0.001
	Mild pain (1-3)	59 (57.8%)	56(4.70%)		115(52.2%)	
	Moderate pain (4-6)	26(25.4%)	03(2.50%)		29(13.2%)	
	Severe pain (7-9)	01(01%)	01(0.80%)		02(001%)	
7.	Cumulative pain score at 24 hours(VAS +NPS)					
	No pain=0	05(4.9%)	13(11.0%)	34.78	18(8.20%)	<0.001
	Mild pain (1-3)	39(38.2%)	83(70.3%)		122(55.5%)	
	Moderate pain (4-6)	52(51.0%)	19(16.1%)		71(32.3%)	
	Severe pain (7-9)	06(5.90%)	03(2.50%)		09(4.1%)	
8.	Cumulative pain score at 48 hours(VAS +NPS)					
	No pain=0	10 (9.8%)	44 (37.3%)	41.37	54(24.5%)	<0.001
	Mild pain (1-3)	56 (54.9%)	67 (56.8%)		123(55.9%)	
	Moderate pain (4-6)	33 (32.4%)	06 (5.1%)		39(17.7%)	
	Severe pain (7-9)	03 (2.9%)	01 (0.8%)		04(1.80%)	

VPIS: Verbal Pain Intensity Scale

VAS: Visual Analogue Scale

NPS: Numeric Pain Scale.

group and 102(46.4%) patients in the placebo group. The duration of surgery ranged from less than 2 hours to more than 6 hours with 171(77.7%) cases having duration of surgery less than 2 hours. The distribution according to the specialty was general surgery 65(29.5%), orthopaedics 56(25.5%), urology 62(4.5%), ear, nose and throat (ENT) 10(28.2%), oral and maxillofacial surgery 5(1.4%), plastic

surgery 3(2.3%) and neurosurgery 19(8.6%).

All pain scales were applied at 24 and 48 hours post-surgery (Figure-2). The difference between the two groups was significant for all the categories ($p < 0.05$) except VAS at 48 hours (Table-2).

All pain scores showed reduced mean values in the test

Table-3: Comparison of mean pain scores between placebo and test group by independent samples T test.

#	Pain scales	Placebo group (n =102)	Test group (n =118)	F Sig.	T score	P value
1.	Verbal pain intensity scale at 24 hours	1.92 ± 0.86	1.19 ± 0.76	0.199	-6.66	<0.001
2.	Verbal pain intensity scale at 48 hours	1.06 ± 0.91	0.86 ± 0.86	0.274	-1.63	0.104
3.	Visual analogue scale at 24 hours	3.70 ± 1.80	2.19 ± 1.44	0.16	-6.79	<0.001
4.	Visual analogue scale at 48 hours	2.96 ± 1.83	1.58 ± 1.12	<0.001	-6.60	<0.001
5.	Numeric pain intensity scale at 24 hours	4.58 ± 1.87	2.97 ± 1.61	0.19	-6.83	<0.001
6.	Numeric pain intensity scale at 48 hours	3.58 ± 1.77	1.98 ± 1.29	<0.001	-7.71	<0.001
7.	Cumulative pain scale at 24 hours (VAS+NPS)	3.43 ± 1.80	1.92 ± 1.57	0.225	-6.64	<0.001
8.	Cumulative pain scale at 48 hours (VAS+NPS)	2.55 ± 1.73	0.94 ± 1.22	0.000	-7.86	<0.001

VAS: Visual Analogue Scale

NPS: Numeric Pain Scale.

Table-4: Comparison of mean pain scores by duration of surgery (one way ANOVA).

#	Pain score	Duration of surgery (Mean ± Standard Deviation)			p value
		<2 hours (n=171)	2-6 hours (n=42)	>6 hours (n=07)	
1.	Placebo group				
	VPIS 24 hours	1.88 ± 0.91	2.13 ± 0.68	1.60 ± 1.14	0.34
	VPIS 48 hours	0.96 ± 0.90	1.25 ± 0.84	1.60 ± 1.14	0.16
	VAS 24 hours	3.41 ± 1.70	4.42 ± 1.74	4.40 ± 2.60	0.038
	VAS 48 hours	2.74 ± 1.68	3.54 ± 1.95	3.40 ± 2.88	0.15
	NPS 24	4.37 ± 1.88	5.21 ± 1.52	4.60 ± 2.70	0.16
	NPS 48	3.48 ± 1.70	3.92 ± 1.86	3.40 ± 2.51	0.56
	Mean cumulative of 24hours (VAS +NPS)	3.14 ± 1.76	4.17 ± 1.46	4.01 ± 2.83	0.03
	Mean cumulative of 48hours (VAS +NPS)	2.37 ± 1.65	3.05 ± 1.78	2.78 ± 2.42	0.24
2.	Test group				
	VPIS 24 hours	1.14 ± 0.62	1.28 ± 1.12	2.50 ± 2.12	0.037
	VPIS 48 hours	0.87 ± 0.78	0.83 ± 1.20	1.00 ± 1.41	0.96
	VAS 24 hours	2.01 ± 1.25	2.78 ± 1.80	5.50 ± 2.12	<0.001
	VAS 48 hours	1.47 ± 0.86	2.11 ± 1.90	2.50 ± 2.12	0.04
	NPS 24	2.83 ± 1.49	3.44 ± 1.88	6.00 ± 1.41	0.008
	NPS 48	1.84 ± 1.09	2.56 ± 1.91	4.00 ± 0.00	0.007
	Mean cumulative of 24hours (VAS +NPS)	1.78 ± 1.44	2.27 ± 1.87	5.42 ± 1.02	0.003
	Mean cumulative of 48hours (VAS +NPS)	0.80 ± 0.99	1.51 ± 1.96	2.37 ± 1.22	0.019
3.	Overall for all the patients				
	VPIS 24 hours	1.46 ± 0.82	1.76 ± 0.89	1.86 ± 1.34	0.084
	VPIS 48 hours	0.91 ± 0.83	1.07 ± 1.02	1.43 ± 1.13	0.198
	VAS 24 hours	2.61 ± 1.67	3.71 ± 1.92	4.71 ± 2.36	<0.001
	VAS 48 hours	2.01 ± 1.42	2.93 ± 2.04	3.14 ± 3.54	0.001
	NPS 24	3.49 ± 1.83	4.45 ± 1.90	5.00 ± 2.38	0.002
	NPS 48	2.54 ± 1.60	3.33 ± 1.98	3.57 ± 2.07	0.011
	Mean cumulative of 24hours (VAS +NPS)	2.36 ± 1.72	3.36 ± 1.88	4.41 ± 2.44	<0.001
	Mean cumulative of 48hours (VAS +NPS)	1.47 ± 1.52	2.39 ± 1.99	2.66 ± 2.05	0.002

VPIS: Verbal Pain Intensity Scale

VAS: Visual Analogue Scale

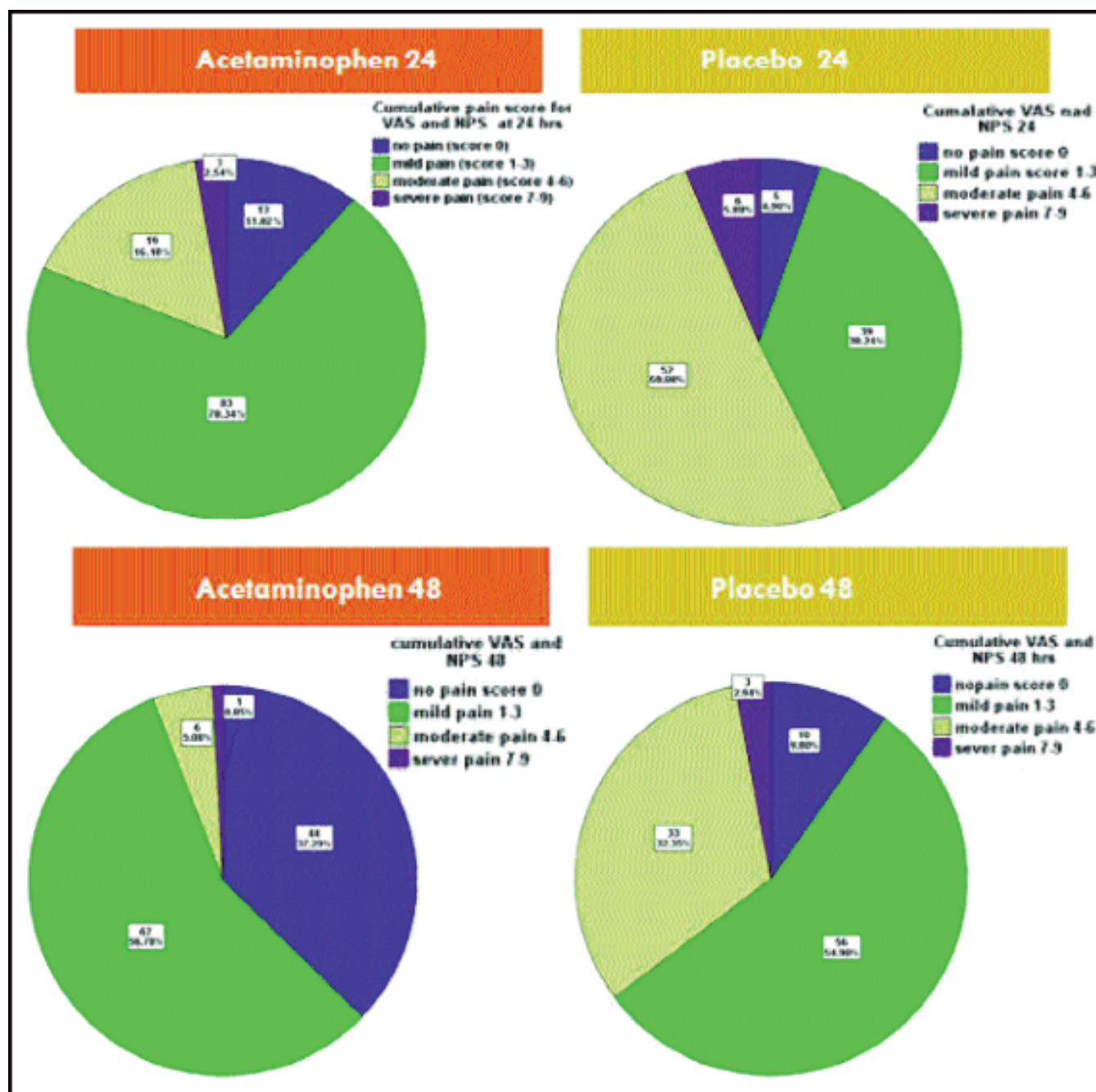
NPS: Numeric Pain Scale.

group, except VPIS at 48hours ($p < 0.05$). An overall increase in mean pain score was observed from VPIS through VAS to NPS in the placebo group whereas much smaller variations in the different pain scale scores were seen in the test group (Table-3).

Mean pain scores increased with duration of surgery, particularly with VPIS and NPS which are more objective scales. An overall pain reduction was seen at 48hours with all pain scales most prominently seen in the cumulative pain scores. Though the number of patients with surgery

PAIN PROFORMA	
Name _____	Age _____ Sex _____ Weight _____ Height _____
Ward _____	Consultant _____ <u>Speciality</u> _____
1. Name of <u>Surgery</u> performed.	
2. Post operative <u>Day</u> .	
3. Duration of Surgery *less than 2 hours* between 2-6 hours *more than 6 hour.	
4. Acetaminophen 1gm (per oral).	
a. ODs.	
b. BD.	
c. TDS.	
Rate the scale of your pain after surgery	
Verbal pain Intensity Scale	Visual Analogue Scale
0-10 Numeric pain scale	

Figure-2: Pain threshold was recorded twice on pain pro forma.



VAS: Visual Analogue Scale
NPS: Numeric Pain Scale

Figure-3: Cumulative scale frequency of control group and test group in first 24 hours and 48 hours.

of more than 6 hours duration was only 7(3.2%), their higher scores tended to affect the pain control achieved in the test group (Table-4).

Cumulative NPS+VAS pain score for both the groups at 24 hours and 48 hours was also calculated (Figure-3).

Discussion

Pain is an essential affective reflex. The four major processes for the pain perception are transduction, transmission, modulation and perception. The pain receptors are stimulated by a noxious event and carried

by delta A, beta and C fibres that synapse with secondary afferent neurons in the dorsal horn of spinal cord. From here it is further carried in spinothalamic tract and spinoreticular tract.

In May 2003, The British Pain Society (BPS) and the Royal College of Anaesthetists (RCOA) in a joint statement stated that the medical personal, nursing and pharmacy staff should be educated about the pain management. Support services must be well-established and well organised and all staff should be trained.

WHO analgesic ladder is a framework used to guide the pharmacological treatment of pain in chronic pain and palliative care patients. In step 1, paracetamol and non-steroidal anti-inflammatory drugs (NSAID) are used followed by weak opioids and strong opioids.⁶ Due to many objections and criticism,⁷⁻⁹ WHO made new changes to the analgesic ladder. The new adaptations is for the relief of acute pain, chronic non-cancer patients and for cancer patient pain. The new ladder integrates fourth step into the ladder which includes invasive technique and neurolysis. It can be used for acute pain in postoperative situation.

This randomised control trial was planned on the observation that far too many people in the postoperative period suffered from various level of pain.³ It was then hypothesised that this pain was in fact the breakthrough pain that occurred between the two doses of parenteral analgesia.

Generally, the analgesia that is used in postoperative period in this surgical setting was ketorolac tromethamine. It is generally a safe NSAID with moderate analgesic potential. It acts peripherally,¹⁰ its peak serum concentration reaches between 20 to 60 minutes and half-life is between 4 and 6 hours.¹¹ Its bioavailability range is from 80% to 100%,¹¹ it binds to plasma protein and has a mean volume distribution of 0.13 to 0.25L/kg. Further, 70% to 72% of the drug metabolite is excreted in urine.¹²

While second dose of ketorolac tromethamine was given at 6hour duration, clearly the ketorolac alone was not sufficient to provide complete analgesia to the patients as shown in the previous study.³ Hence it was hypothesised that we need to give another analgesic agent to provide better pain control. In order to accomplish that acetaminophen was selected as the drug of choice.

Acetaminophen is a safe analgesic agent.¹³ It is a weak cyclooxygenase (COX)-1 and COX-2 inhibitor. Orally administrated acetaminophen is rapidly absorbed

through the gastrointestinal (GI) tract. Peak blood concentration of acetaminophen reaches in 30 to 60 minutes.¹⁴ Bioavailability is 70% to 90% which is dose-dependent. It distributes rapidly throughout most body tissues and fluids and has volume distribution of approximately 0.9 L/kg. It binds to plasma protein and predominantly metabolises in liver. In the first 24 hours, 85% to 95% of therapeutic dose is excreted in urine. Plasma half-life is 1.9-2.5 hours and total body clearance is 4.5 to 3.5 ml/kg/min.¹⁵ There is little effect of age on plasma half-life. Side effects of acetaminophen include low fever with nausea, stomach pain and loss of appetite, jaundice and liver cirrhosis in case of overdose.

With acetaminophen as the interventional drug, it was administered at two-hour duration following the ketorolac tromethamine induction. Pain score was then recorded two hours following the induction. To record the pain after these two drugs, pain scales were used.

Pain rating scales take an important place in clinical practice. Three international validated pain scales were used in this study including VIPS, NPS and VAS. VIPS is the simplest of all pain scales and is sometimes liable to be misinterpretation.¹⁶ NPS is most commonly used and it can be recorded graphically as well as verbally. It has poor reproducibility and has a failure rate of 2%. VAS is more reliable when used horizontally or vertically. VAS scores are reproducible and reliable to the confidence interval (CI) 95%. Failure rate is 4% to 11%. VAS and NPS have strong correlation; VIPS and VAS have significant correlation at a lower score.

In order to remove the bias during recording, double blinding and placebo was used. The data was recorded twice in 48 hours. The test group and the placebo groups were then compared which clearly showed the effectiveness of acetaminophen in results.

The results of the test group showed that far too many people were still suffering from various degrees of pain following surgery. While acetaminophen in combination with ketorolac tromethamine did decrease the number of patients who experienced moderate to severe pain, the number of patients who were in mild pain increased. It probably happened because these two analgesic agents shifted the patients with moderate to severe pain to mild category. Hence, while acetaminophen was effective in decreasing the intensity of pain, but in combination with ketorolac tromethamine failed to achieve complete analgesia. In fact, only 11.02% patients

were without pain in the first 24 hours. The figures improved, in the next 24 hours when 37% patients reported no pain.

Conclusion

It was partially proven that pain in our cohort of patients was probably due to breakthrough pain between the parenteral analgesic doses. Also, the regime normally used even with additional dosage of acetaminophen was insufficient to control pain. We need to develop and further refine our policy of pain control in the postoperative period. Our aim should be to achieve complete analgesia in postoperative period for all our patients.

Disclaimer: Our institution was unable to obtain an RCT number for this manuscript.

Conflict of Interest: None.

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