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An Evaluation and comparison of the various preparations of intravenous injection, Transdermal patch and rectal suppository of diclofenac sodium in the pain management after gynaecological surgery: A randomized trial

KEYWORDS: Gynaecological surgery, Diclofenac sodium, Transdermal patch, Rectal suppository

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ABSTRACT *Objective: To evaluate and compare the various preparations of intravenous injection, Transdermal patch and rectal suppository of diclofenac sodium in the pain management after gynaecological surgery.*

Methods: This study was a randomized clinical trial. Hundred ASA grade I female patients between 18-70 years of age scheduled for major gynaecological surgery were included in the study divided in four groups (25 patients in each group). Group I received 100 mg rectal suppository of diclofenac, Group II receive 200 mg rectal suppository of diclofenac, Group III receive 75 mg intravenous injection diclofenac and Group IV received 200 mg transdermal dermal patch of diclofenac.

Results: The baseline data was comparable among the groups. There was significant difference in the hemodynamic parameters after post-op and subsequent time intervals. However, minor difference was observed among the groups in serum creatinine and hemoglobin. Nausea was observed to be higher in Group I & II than Group III & IV. However, vomiting was lower in Group III than Group I, II and IV.

Conclusion: In country like India where the anti narcotic act very much prevalent, the NASAID (like Transdermal patch and rectal suppository of diclofenac) are best drugs for postoperative pain control.

INTRODUCTION

One of the most common symptoms for which a patient seeks medical advice is pain. The International Association for the study of pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage". Postoperative pain is a unique and common form of acute pain. Although ample evidence indicates that an efficacious postoperative pain treatment reduces patient morbidity and patient outcome, recent studies demonstrate that about 50–70% of patients experience moderate to severe pain after surgery indicating that postoperative pain remains poorly treated. The management of postoperative pain is an essential and integral part of the care given to the patient that assumes an important role in transition from the recovery unit to the home environment (Samal et al, 2013).

Effective postoperative pain control is an essential component of the care of the surgical patient. Various types drugs are used for postoperative analgesia, of which narcotics and NSAIDS are the most important ones. Narcotics are known to cause drowsiness, constipation, urinary retention, haemodynamic and respiratory disturbances as compared to minimal side effects by NSAIDS. Diclofenac is one of the most commonly used NSAID. Oral administration is the route of choice in daily practice but it becomes impractical before and after surgery because of high first pass metabolism. Its parenteral preparation is irritating and hence it is very painful at the site of administration. Development of skin, subcutaneous and even muscle tissue necrosis (Nicolau syndrome), abscess formation, etc. are rare but serious complications of intramuscular injections of NSAIDS (Lie et al., 2006). As the understanding of pain pathophysiology and treatment is increasing, new routes of drug delivery are being discovered with the objective of attempting to block pain at peripheral sites, with maximum active drug and minimal systemic effects. Topical (Transdermal) preparations are the result of such exploration, which are expected to be free of the drawbacks of oral, parenteral diclofenac. Administration is also very simple, noninvasive and only once in 24 hrs (Prausnitz et al., 2004; Scheindlin, 2004).

Diclofenac is an analgesic-antipyretic-antiinflammatory drug. It inhibits prostaglandin synthesis by inhibiting cyclooxygenase enzyme. Though parenteral diclofenac (Intramuscular) have been used most often, suppository and intravenous use is also possible. It can be administrated by Transdermal route also. The advantages of this route are painless, non-irritant, increased bioavailability and it can be applied for 24 hours (Gschwend et al, 2005). Though, transdermal route has its own advantages, there are no studies to compare this route along with intramuscular route.

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The present study was designed to evaluate and compare the various preparation of intravenous injection, Transdermal patch and rectal suppository of diclofenac sodium in the pain management after gynaecological surgery.

MATERIAL AND METHODS

This study was a randomized clinical trial conducted in the Department of Anesthesiology and Intensive care in a tertiary care hospital in north India from May 2007 to June 2009. Prior to commencing the investigation, approval was obtained from both the Ethical and Hospital Research Committee.

Patients to this study were explained about the objective of the study and informed consent was taken. Hundred ASA grade I female patients between 18-70 years of age scheduled for major gynaecological surgery were included in the study. Patients with known allergic history to diclofenac or any NSAID, history of gastrointestinal bleeding or peptic ulcer, history of asthma, history of renal failure, patient on anticoagulant or with history of bleeding tendency, pregnant or lactating mother, contraindications for oral medication, immediate admission required for further management and concomitant treatment of diclofenac during the previous 24 hours were excluded from the study. No premedication was given in any case.

Patients were randomly assigned to four groups using computer generated table of 25 each as follows: Group I received 100 mg rectal suppository of diclofenac, Group II receive 200 mg rectal suppository of diclofenac, Group III receive 75 mg intravenous injection diclofenac and Group IV received 200 mg transdermal dermal patch of diclofenac.

Methods

The dose of analgesic was given to the patients at the time of start of surgery. In intravenous group, patients received 75 mg diclofenac in 100ml, 0.9% saline was infused over 30 minutes. In patients who received 200 mg diclofenac dermal patch applied on non hairy area (front of chest). In patient received diclofenac suppository (100mg and 200mg), hold it between thumb and middle finger, with the tapered end facing away from the palm of hand. The tip of index finger was rest on the flat end of the suppository. Placed the tapered end of the suppository on the rectum. Gently, pushed the suppository with index finger into the rectal opening. Continued pushing it until index finger clears the sphincter, then removed index finger, leaving the suppository in. If did not insert in far enough, the suppository slides backed out.

In the operation theatre, patient inquired for 8 hrs fasting period and was being asked to void the bladder. Intravenous access was established using an 18 gauge cannula. All patients were monitored using pulse oxymeter- continuous recording, ECG Continuous recording and NIBP every 2-5 min interval.

A 25 G spinal needle (Quincke) was introduced in the same space till free flow of CSF occurred following which 3 ml 0.5% bupivacine heavy was given. Then the spinal needle was taken out.

Heart rate and blood pressure were assessed every 5 min for first 3 minute and then every 15 min. Hypotension was marked if the systolic blood pressure gone below 90mmHg or 20% below at baseline. The hypotension was corrected with intravenous infusion of colloid and/or with incremental dose of ephedrine. O^2 saturation was measured every 15 min and visual analogue scale (VAS) was done using a visual analogue scale (VAS) of 0-10cm (0 with= no pain and 10=severe pain) recommended. The possible complications were noted.

Statistical analysis

The results are presented in mean±SD and percentages. The Chi-square test was used to compare the categorical variables. The one way analysis of variance followed by Tukey's post-hoc tests was used to compare the discrete variables among the groups at various time periods. The repeated measures of analysis of variance was used to find the effect of time X groups interactions on the study parameters. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

RESULTS

There was no significant (p>0.05) difference in the age and weight of patients among the groups showing the comparability of the groups in terms of age and weight (Table-1).

The baseline HR was almost (p>0.05) equal in all the four groups. At 10 minutes, the HR among four groups was significantly different almost rose to 80 in Group I, II and IV. There was a decline in the HR at 30 minutes which reduced to 75.48 ± 3.13 in Group I, 72.72 ± 1.45 in Group II, 74.00 ± 4.55 in Group III and 76.48 ± 2.84 in Group IV. It further declined at 1 hour in Group I, II and IV but increase to 80.68 ± 2.65 in group III. The repeated measures of analysis of variance revealed that there was significant interaction effect of time X Groups (p=0.001) on HR variability (Fig.1).

There was no significant (p>0.05) difference in SBP and DBP at baseline among the groups. SBP values increased to 132.96 ± 4.73, 134.16 ± 3.78, 136.00 ± 6.73 and 134.00 ± 5.53 in Group I, II, III and IV respectively at 10 minutes after induction and decreased at 30 minutes to 123.52 ± 5.23, 127.92 ± 4.63, 122.48 ± 4.62 and 123.36 ± 5.64 respectively. After 1 hour, the mean SBP value was observed to be 124.24 ± 4.63, 123.84 ± 5.09, 129.52 ± 3.33 and 125.52 ± 5.04 in Group I, II, III and IV respectively. Similar increase/decrease was found for DBP. The repeated measures of analysis of variance revealed that there was significant interaction effect of time X Groups (p=0.001) on SBP and DBP variability (Table-2)

The value SPO_2 was observed to be almost similar among the groups at different time intervals. The repeated measures of analysis of variance revealed that there was no significant interaction effect of time X Groups (p>0.05) on SPO_2 variability (Fig.2).

Mean VAS score was observed to be higher in Group III & IV than Group I & II at 1 hour follow up. At 6 hour, it increased to 4.72±0.61, 4.52±0.51, 5.80±0.64 and 4.72±0.61 in Group I, Group II, and Group IV respectively. The mean scores declined to 3.20±1.41, 2.40±1.35, 4.48±0.71 and 3.76±1.01 at 12 hour in Group I, Group II, and Group IV respectively. The repeated measures of analysis of variance revealed that there was no significant interaction effect of time X Groups (p>0.05) on VAS variability (Fig.3).

At baseline, serum creatinine and hemoglobin were similar among the groups (p>0.05). The serum creatinine was observed to be significantly different among the groups at 24 hour. However, the change in serum creatinine was not statistically significant (p>0.05) in all the four groups. There was no significant (p>0.05) difference in hemoglobin

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among the groups at 24 hour (Table-3).

Nausea was observed to be higher in Group I & II than Group III & IV. However, vomiting was lower in Group III than Group I, II and IV (Fig.4).

DISCUSSION

Postoperative pain may result in psychological, physiological, neuroendocrine, respiratory and cardiovascular problems ultimately increasing the risk of postoperative morbidity and mortality. Effective control of postoperative pain remains one of the most important & pressing issues in the field of anaesthesia. Non-steroidal anti-inflammatory drugs (NSAIDS) are being very widely used either alone or in combination with opioids for postoperative analgesia.

As the understanding of pain pathophysiology and treatment increases, new routes of drug delivery are being discovered with the objective of attempting to block pain at peripheral sites, with maximum active drug and minimal systemic effects. Topical preparations are the result of such exploration. The goal of topical NSAIDs is to minimize systemic adverse effects and encourage compliance. Most topical preparations are available as transdermal patches, ointments, or creams. Based on contents, there are two primary types of analgesic patches: 1) Patches containing counterirritants-contain ingredients such as capsaicin, methyl salicylate, camphor, or menthol, which are thought to mask pain signals by causing other sensations (itching, warmth, or cooling) in the areas they are applied to. 2) Patches containing narcotics or NSAIDS- e.g. fentanyl, Buprenorphine and diclofenac patch.

The present study was conducted on 100 female of ASA grade 1 between 18-70 years of age to evaluate and compare the preemptive effect of diclofenac rectal suppository, transdermal patch and intravenous injection on postoperative pain in patients scheduled for elective major gyenacological surgeries (hysterectomy).

In this study, the mean age and weight were comparable among themselves and hence statistically insignificant ($p>0.05$). The Heart rate, Systolic and Diastolic blood pressure comparison among the four groups were statistically insignificant ($P>0.05$) during intraoperative period except for a few readings which can be attributed to the effect of anaesthesia and anxiety during surgery.

The comparison of heart rate, systolic blood pressure, diastolic blood pressure among group I vs III, group II vs III and IV vs III were significant in the postoperative period showing that the patients in group III were having pain and hence haemodynamically unstable. It has been shown that patients taking diclofenac suppository were significantly less likely to experience pain at 24 hour. (Dodd JM etal, 2004).

Patients receiving 75 mg of diclofenac do not having morphin showed that changes were significant after one hour postoperative period suggesting that pain relief in suppository 100 mg group were better and extended for 24 hours and Intavenous diclofenac 75 mg giving very poor analgesia compare to suppository in early postoperative period and late postoperative period. Mean pain intensity at 12 hour and 24 hour after surgery was significantly lower in diclofenac trans dermal patch. The finding of this study is similar to the study by Franco et al (2005).

In the present study, comparison of mean Visual Analogue score in Group III vs Group IV over 24 hour postoperatively showed that the difference was statistically significant. This shows that diclofenac Transdermal patch is good for postoperative period over 24 hours. In our study, mean VAS was statistically significant in Group III vs II over 24 hour, this shows that suppository 200 mg is also better in pain relief than diclofence intravenous in early as well as late postperative period. While comparing Group I and II, statistically significant results was observed after 6 hour postoperative period for 24 hour except for few readings practically of no value, this shows that the suppository 200 mg was definitely better in pain relief while suppository and group IV data was statistically non significant for 24 hour except few readings in early postoperative period in favor of diclofenac suppository this shows diclofenac 200 mg dermal patch is comparable to diclofenac suppository 200 mg in late postoperative period. Patients using suppository had less side effects, discharged earlier. Diclofenac suppository is an effective, safe, costeffective practical and way of providing postoperative analgesia (Lubna and Manzar, 2004). Bhargava et al (2015) concluded that Diclofenac sodium patch was as effective as Diclofenac sodium intramuscular injection in providing post operative analgesia. Only concern about patch was that it has longer onset of action, so if applied by proper planning; patch had many advantageous.

In this study, the incidence of hypotension was lowest in the suppository 200 mg. The incidence of pruritis was lower in diclofenac 100 mg suppository. Vomiting was also low in suppository 200mg except few readings may be due to effect of surgery or anaesthesia. Patient in suppository 100mg group were having higher incidence of hypotension. This may be due to anesthesia, surgery or fluid volume status of patients. Abdominal surgery may predispose nausea, vomiting. Effect on renal profile after 24 hour NSAID therapy is insignificant (Lee and Cooper, 1999). Since, diclofenac reaches its peak plasma levels within 20-60mins, allowing adequate time for pain relief to take effect is very important for the accurate evaluation of drug effectiveness in studies performed using rectal diclofenac (Cengiz et al, 2015).

In our study, effect on serum creatinine and Hb in all groups were insignificant. From this study, we conclude that 200 mg diclofenac suppository provides better pain relief in postoperative period and effect of diclofenac 200 mg trans dermal patch is almost same to 200 mg rectal suppository with good acceptability. The effect of intravenous 75 mg diclofenac is not good for postoperative pain relief as compaire to diclofenac suppository 200 mg and 100 mg and Transdermal patch 200 mg of diclofenac.

CONCLUSION

In country like India where the anti narcotic act very much prevalent, the NASAID (like Transdermal patch and rectal suppository of diclofenac) are best drugs for postoperative pain control.

Conflict of interest: None
Funding: None

Table 1: Distribution of cases according to age and weight in various groups

	Group I	Group II	Group III	Group IV	p-value[1]
Age (years)	38.48 ± 10.08	36.84 ±9.07	41.60 ± 6.91	41.60±10.12	0.176
Weight (kg)	51.40 ± 5.09	52.52 ±3.02	53.36 ± 4.59	51.68±6.30	0.408

[1]ANOVA test

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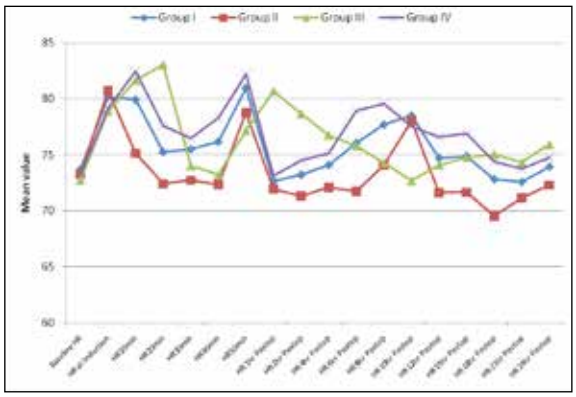

Fig.1: Comparison of heart rate among the groups at time intervals

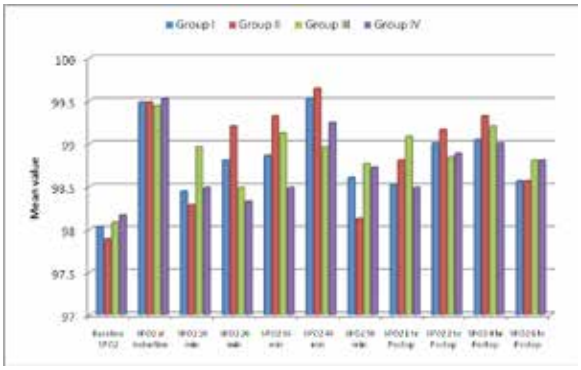

Fig.2: Comparison of SPO_2 among the groups at time intervals

Table-2: Comparison of SBP and DBP among the at time intervals

Time interval	SBP (mmHG)				DBP (mmHG)			
	Group I	Group II	Group III	Group IV	Group I	Group II	Group III	Group IV
Baseline DBP	120.16 ± 7.30	123.84 ± 5.09	122.80 ± 685	120.40 ± 8.60	68.24±6.64	67.76±3.33	70.64±4.99	70.32±8.84
At Induction	126.40 ± 6.11	128.08 ± 3.85	129.28 ± 5.99	127.52 ± 2.70	74.00±6.48	73.36±3.54	75.12±1.74	75.84±8.71
10min	132.96 ± 4.73	134.16 ± 3.78	136.00 ± 6.73	134.00 ± 5.53	78.64±4.11	78.16±3.15	78.16±2.70	79.92±5.14
20min	127.84 ± 5.28	130.56 ± 4.30	125.28 ± 3.41	127.60 ± 5.35	74.88±6.53	74.40±3.36	74.80±2.82	76.88±8.73
30min	123.52 ± 5.23	127.92 ± 4.63	122.48 ± 4.62	123.36 ± 5.64	73.36±4.99	71.28±1.90	73.04±2.52	75.92±5.70
40min	125.04 ± 3.89	125.52 ± 4.05	123.84 ± 5.65	123.44 ± 4.8	74.48±4.62	73.68±3.90	71.12±2.45	74.88±4.32
50min	125.92 ± 3.89	127.92 ± 2.12	126.48 ± 4.90	125.44 ± 4.88	77.04±3.47	75.76±3.38	75.12±2.71	77.84±3.46
1hr Postop	124.24 ± 4.63	123.84 ± 5.09	129.52 ± 3.33	125.52 ± 5.04	74.56±2.55	73.68±2.28	74.48±2.46	75.20±3.58
2hr Postop	125.28 ± 3.36	125.84 ± 3.26	128.48 ± 3.22	124.40 ± 3.46	71.12±5.35	67.92±3.39	75.60±2.16	73.68±5.02
4hr Postop	124.24 ± 3.52	124.24 ± 4.09	127.60 ± 2.44	124.96 ± 2.77	69.68±6.52	71.28±1.62	76.40±3.21	70.32±8.84
6hr Postop	125.20 ± 4.65	126.56 ± 4.02	127.36 ± 1.80	123.12 ± 3.83	73.20±3.36	73.52±1.93	76.16±2.88	73.84±3.91
8hr Postop	124.00 ± 4.16	122.40 ± 2.94	1.27.44 ± 2.04	125.60 ± 4.47	73.12±3.37	72.64±3.63	76.32±3.72	73.52±3.17
10hr Postop	124.96 ± 4.32	124.40 ± 3.60	129.36 ± 2.87	125.60 ± 4.16	73.60±3.16	72.00±1.63	76.80±2.88	74.64±3.40
12hr Postop	123.44 ± 3.72	122.00 ± 2.88	128.00 ± 1.82	124.24 ± 4.25	73.36±2.93	70.40±2.16	75.36±1.60	74.48±2.25
15hr Postop	122.24 ± 4.17	119.52 ± 4.13	127.36 ± 1.60	124.88 ± 3.27	73.60±5.74	69.36±2.49	75.60±3.05	76.88±5.71
18hr Postop	122.00 ± 4.12	121.12 ± 5.26	126.56 ± 4.06	123.76 ± 2.40	72.80±2.44	72.00±1.82	75.36±2.43	73.82±2.57
21hr Postop	122.48 ± 2.66	122.40 ± 2.94	124.88 ± 3.05	122.96 ± 2.71	73.84±4.09	73.12±2.08	75.68±1.70	73.28±5.68
24hr Postop	123.20 ± 3.05	122.56 ± 2.80	126.24 ± 3.12	123.28 ± 3.55	69.36±5.76	70.64±3.30	74.88±2.08	69.92±7.05

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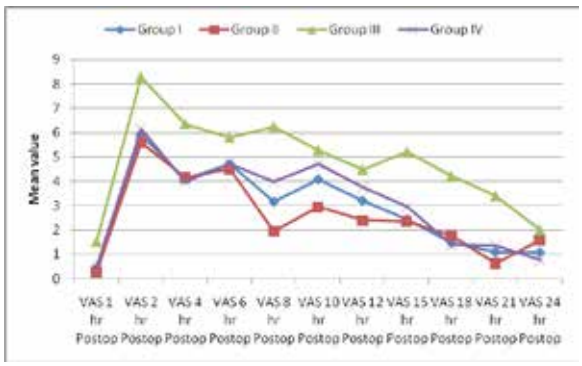

Fig.3: Comparison of VAS among the groups at time intervals

Table-3: Comparison of biochemical parameters among the groups

	Group I	Group II	Group III	Group IV	p-value[1]
Serum creatinine					
Baseline	0.86 ± 0.26	0.73 ± 0.13	0.74 ± 0.16	0.76 ± 0.16	0.06
At 24 hour	0.76 ± 0.17	0.74 ± 0.14	0.75 ± 0.13	0.71 ± 0.14	0.01*
Hemoglobin					
Baseline	11-28 ± 0.98	11.54 ± 1.11	11.36 ± 1.06	11.26 ± 1.49	0.11
At 24 hour	11.62 ± 0.99	11.34 ± 1.53	11.62 ± 1.10	11.14 ± 1.41	0.10

[1]ANOVA test

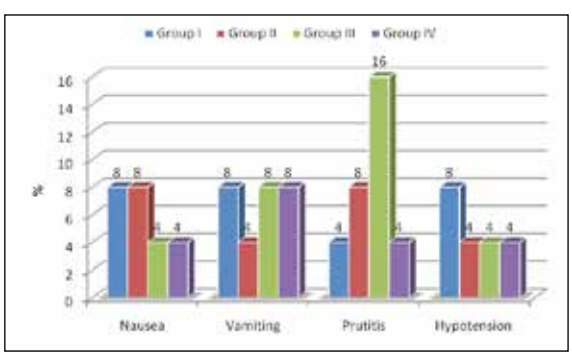

Fig.4: Comparison of adverse effects among the groups (Chi-square p=0.07)

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