



**ORIGINAL RESEARCH PAPER**

**Pharmacology**

**COMPARATIVE EFFICACY, TOLERABILITY AND SAFETY OF TRAMADOL AND NSAIDS IN POSTOPERATIVE PAIN, AN OBSERVATIONAL STUDY.**

**KEY WORDS:** Analgesia, Opioids, Adverse effects

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**ABSTRACT**

Adult male patients of age 25-55 years, undergone surgery for hydrocele, inguinal hernia and haemorrhoids (n=594) were enrolled for comparative analysis of efficacy and safety of tramadol and NSAID in postoperative period. The drugs prescribed were diclofenac, ibuprofen, indomethacin and tramadol. The analgesic effect reported from 3rd day onward (all drugs) in few and covered remaining patients up to day 5 by diclofenac, indomethacin; up to day 6 by ibuprofen, tramadol. Analgesic efficacy observed as: Indomethacin > Diclofenac > Ibuprofen > Tramadol. Adverse effects manifested as gastric (n=55) due to NSAID and neurological (n= 39) due to tramadol. All adverse effects were mild, well tolerated, required no discontinuation of treatment. Postoperative recovery was satisfactory.

**INTRODUCTION**

Postoperative pain is explained as unpleasant sensory and emotional experience, associated with tissue damage (trauma, surgery; including compression, ischaemia)<sup>1</sup> For most patients, the immediate postoperative period is the time of transition to normal neurophysiological function with treatment of pain and other symptoms, being relatively common<sup>2</sup>. Postoperative pain adds to agony, anxiety, restlessness, loss or disturbance of sleep etc. It has been reported that pain is poorly evaluated and undertreated<sup>3</sup>, hence persistent or inadequate pain relief may delay recovery, prolong hospital stay which may raise doubt of surgical skill. Pain management is therefore an essential therapy. Non-steroidal analgesic, anti-inflammatory + antipyretic drugs (NSAID) and opioid analgesics are mainstay as pain reliever<sup>4</sup>. The drugs used should aim at early and effective pain relief, minimal adverse effects (AE), and no drug-drug or drug-disease interactions. Tramadol is a synthetic codeine analogue (opioid analgesic), indicated in mild to moderate pain<sup>5</sup>. There is no significant risk of addiction with short term use of tramadol for postoperative pain management. Respiratory depression appears to be less than equianalgesic doses of morphine and is reversible by naloxone. The degree of constipation is less than that seen after equivalent doses of codeine.<sup>6</sup> NSAID are associated with many systemic adverse effects (gastric ulcer; bleeding, renal injury)<sup>3</sup>; also there is a risk of drug interactions<sup>5</sup>, so in few patients even for a short period, NSAID may not be suitable or may need to discontinue. Opioid analgesics are other group preferred by some surgeons, the advantage being hypnosis with analgesia and the AE like NSAID do not occur<sup>3</sup>.

**AIM:**

To Assess comparative efficacy and adverse effects of tramadol & NSAIDS

**MATERIALS AND METHODS:**

**Inclusion Criteria:**

Total (n=594) Adult male patients of age 25- 55 years, operated under spinal anaesthesia (for hydrocele, hernia, haemorrhoids)

**Exclusion criteria :-**

- 1) Patients giving H/O backache

- 2) History suggestive of allergic diseases, drug hypersensitivity/peptic ulcer
- 3) Comorbid diabetes mellitus, Coronary artery disease
- 4) Abnormal hepatic, renal function tests/ thyroid profile/lipid profile
- 5) Smokers and regular heavy alcohol consumers.
- 6) Patients exposed to health hazard occupations.
- 7) Patients under psychiatric drug therapy.
- 8) Female patients

This is the prospective observational Study carried out at department of pharmacology, in collaboration with surgery department, government medical college, Akola, from Jan 2017-Dec 2017. The data of adult male patients of age 25- 55 years. (n=594) operated under spinal anaesthesia (for hydrocele, hernia, haemorrhoids) scrutinised and enrolled for the present study. They were divided into 3 age groups (A = 25-35 years, B= 36-45 years. and C=46-55 years.)

On Postoperative day 1, analgesic drugs were prescribed and continued till complete pain relief as follows<sup>4,5,7</sup>:

- 1- Diclofenac sodium 75 mg BD.
- 2) Ibuprofen 400 mg TDS
- 3- Indomethacin 25 mg TDS.
- 4) Cap Tramadol 100 mg BD

Few patients in immediate Postoperative period were given IM Pentazocine, sublingual buprenorphine for severe pain, switched over to one of above drugs after reverting to moderate or mild intensity of pain. The relief of pain assessed on the criteria of visual analogue scale<sup>2</sup>.

**Ethical consideration:** Approved from institutional ethics committee.

**RESULTS**

Data of the recruited patients (n=594) who were undergone surgery under spinal anaesthesia regarding age, diagnosis, analgesic prescribed in PO period with duration, extent of pain relief, adverse effects and tolerability were noted and analysed.

The distribution of age and surgical diagnosis is shown in fig 1

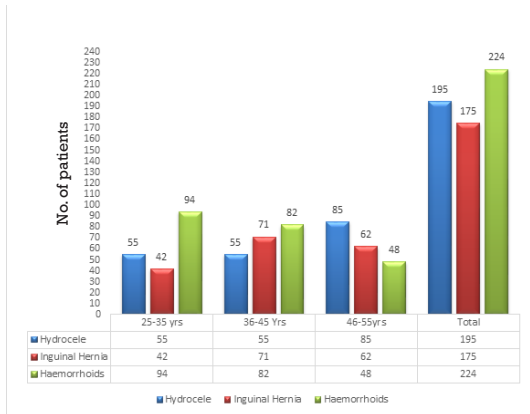


Fig 1 Age and diagnosis s distribution

Drug distribution is shown in table 2.

Table 2- Analgesic drug prescription in postoperative period. (n=)

Age group	Analgesic drug prescriptions (n=)*			
	Diclofenac	Ibuprofen	Indomethacin	Tramadol
A= 25-35	49	50	49	50
B= 36-45	50	49	50	49
C= 46-55	51	50	48	49
<b>Total</b>	<b>150</b>	<b>149</b>	<b>147</b>	<b>148</b>
<b>Percentage</b>	<b>(25.2%)</b>	<b>(25.1%)</b>	<b>(24.7%)</b>	<b>(25%)</b>

\* Drugs given by per oral route

Analgesic effect analysed on diurnal schedule (visual analogue scale)

(as per ward round notes); the complete relief of pain (n=) at perisurgical site observed in term of days is depicted in table 3.

Table 3. Analgesic effect (pain relief) in days among age groups

Age gr (years.)	On day	Diclofenac (n=150)	Ibuprofen (n=149)	Indomethacin (n=147)	Tramadol (n=148)
<b>A (25-35)</b>	3 <sup>rd</sup>	11	10	10	10
	4 <sup>th</sup>	23	12	12	10
	5 <sup>th</sup>	15	12	27	10
	6 <sup>th</sup>	--	16	--	20
	<b>Total</b>		<b>49</b>	<b>50</b>	<b>49</b>
<b>B (36-45)</b>	3 <sup>rd</sup>	09	07	09	08
	4 <sup>th</sup>	18	12	16	12
	5 <sup>th</sup>	23	14	25	14
	6 <sup>th</sup>	--	16	--	15
	<b>Total</b>		<b>50</b>	<b>49</b>	<b>50</b>
<b>C (46-55)</b>	3 <sup>rd</sup>	13	12	11	06
	4 <sup>th</sup>	15	13	14	11
	5 <sup>th</sup>	23	11	23	15
	6 <sup>th</sup>	--	14	--	17
	<b>Total</b>		<b>51</b>	<b>50</b>	<b>48</b>
<b>Drug total n=</b>	3 <sup>rd</sup>	33	29	30	24
	4 <sup>th</sup>	56	37	42	33
	5 <sup>th</sup>	61	37	75	39
	6 <sup>th</sup>	--	46	--	52
	<b>Total</b>		<b>150</b>	<b>149</b>	<b>147</b>
<b>Grand total=594</b>					

We observed that the cumulative pain relief in all subjects (100%). Maximum relief (n=) and the day of therapy observed was:

**Diclofenac** n=61/150 (40.6%) – day 5, **Ibuprofen** n=46/149 (31%) - day 6, **Indomethacin** n=75/147 (51%) - day 5 **Tramadol** n=52/148 (35%) - day 6.

We also observed that diclofenac offered relief in more subjects than indomethacin on day 3 (23.3% vs. 20.4%) and day 4 (37.3% vs. 28.5%).

The three age groups responded to four types of analgesics in the range of 6-27 subjects from day 3 to 6; moreover the response was not consistent with drug and age factor also. Analgesic effect most observed was:

Diclofenac: (3 age gr) 23/150 - age gr A - day 4 & B, C =

23,23/150 - day 5 each; Ibuprofen: (2 age gr) 16/149 - age gr A, B-both day 6; Indomethacin=27/14 - age gr A-day 5 and Tramadol=20/148 - age group A-day 6.

Hence the maximum analgesia as per age group observed was:

**Age group A-** all four drugs,  
**Age group B-** diclofenac, ibuprofen  
**Age group C-** diclofenac.

The analgesic drug therapy discontinued after day 5 or 6 after 100% analgesia achieved, as the case may be. The adverse effects were meticulously noted (as per case records). NSAID's showed gastric AE, tramadol manifested neurological AE, all based on their mechanism of action. These AE's of analgesics given from day 1-day 6 are shown in table 4.

Table 4. Adverse effects of analgesics in postoperative period\*. n=

Adverse effects	Diclofenac (n=150)	Ibuprofen (n=149)	Indomethacin (n=147)	Tramadol (n=148)	Total (n=594)
<b>Gastric</b>					
Nausea	11	07	16	00	34
Vomiting	02	00	04	00	06
Retrosternal burning	05	02	08	00	15=55 12.3%
<b>CNS</b>					
Sedation	00	00	00	17	17
Dizziness	00	00	00	22	22=39 26.3%
<b>Total</b>	<b>18</b>	<b>09</b>	<b>28</b>	<b>39</b>	<b>94</b>

Some patients had more than one AE. All the AE's were mild, well tolerated, subsided with or without appropriate add on drugs. None required discontinuation. Postoperative recovery was satisfactory and uneventful.

**DISCUSSION**

The mechanism of analgesia of NSAID is restriction of synthesis of prostaglandin through inhibition of cyclooxygenase II enzyme (from membrane bound phospholipids)<sup>7</sup> which is the inducible enzyme in response to trauma, infection which next lead to pain, inflammation and fever<sup>7</sup>. Tramadol is analgesic of opioid group, derived from codeine, reported to be effective in mild to moderate intensity of pain<sup>2</sup>. Tramadol is a weak  $\mu$  opioid receptor MOR antagonist; part of analgesia is mediated via inhibition of uptake of norepinephrine and serotonin.<sup>8</sup> The AE's of NSAID are multisystem: gastric, coagulopathy, renal, cardiovascular and so on<sup>5</sup>; these may also occur due to irrational prescription or on long term abuse, short term use if at all causes AE's, are of mild intensity and well tolerable; may not present with serious events<sup>1,2,4</sup>. The AE's of opioids such as nausea, vomiting and retrosternal burning are due to stimulation of central emetic centre and absence of prostaglandin E2.<sup>5</sup> Hypnosedation, dizziness etc. occur due to interference of consciousness, alertness due to MOR blockade. Postoperative patients (n=594) of hydrocele (n=195), hernia (n=175), acute haemorrhoids (n=224), operated under spinal anaesthesia were prescribed both group of analgesic drugs. Data of adult male subjects (age 25-55 years) scrutinized to analyse the comparative efficacy, safety and suitability of prescribed NSAID- diclofenac (n=150), ibuprofen (n=149), indomethacin (n=147) and tramadol, that corroborates the literature<sup>7,8</sup>. The prescription trend is nearly similar (24.7% - 25.2%). It was observed that pain relief to some extent experienced by few subjects within 1-2 hr. which is related to the time of onset of action (analgesia)<sup>5,8</sup>. However it was day 3 onward there was complete relief of pain in some of them, subsequently covered remaining gradually. The drugs prescribed are of equal efficacy similar to literature<sup>7,8</sup>. As far as duration of therapy is concerned, diclofenac and indomethacin imparted pain relief between days 3-5, whereas ibuprofen and tramadol therapy needed one day more (day 3 to 6). Our finding indicate the higher efficacy of former two drugs to relieve PO similar to study<sup>9</sup> which also showed diclofenac more efficacious than tramadol.

In nutshell indomethacin has shown better efficacy as PO analgesic (maximum 51%) with early relief (day 5), followed by diclofenac > tramadol > ibuprofen. The diagnosis, type of surgery, is nowhere related to the quantum and latency of analgesia; however age group 25-35 years showed maximum analgesia with all four drugs, suggest that analgesic action is pronounced in younger age, may be due to better inhibition of cyclooxygenase enzyme and antagonism of MOR, no such information could find.

**Conflict of interest:** Nil

**Limitations:** Females were excluded from the study and only oral route of drug administration were taken into consideration.

**CONCLUSION:**

All the analgesics have exhibited satisfactory analgesia from day 3 onward.

Diclofenac and indomethacin achieved the 100% target analgesia earlier than ibuprofen and tramadol.

Analgesia with all four drugs observed better among age group 25-35 years.

Tramadol is free of gastric and other adverse effects unlike NSAID.

The adverse effects were as mild and tolerable required no discontinuation.

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