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EFFECTIVENESS & SAFETY OF INTRAVENOUS WATER BASED DICLOFENAC SODIUM FOR POST OPERATIVE PAIN MANAGEMENT

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ABSTRACT

OBJECTIVE: This prospective randomized single blind trial was designed to evaluate the efficacy and establish the safety of use of intravenous diclofenac sodium for post operative pain management.

SETTINGS: Department of Anaesthesiology & Surgical Intensive Care Unit, Dow medical College and Civil Hospital, Karachi.

METHODOLOGY: Fifty patients undergoing different types of surgeries were studied. All the patients were followed for 48 hours post operatively. The patients were American Society for Anaesthesiologist Physical Status of I, II or III aged more than 15 years. A standardized anaesthetic technique consisting of thiopentone-suxamethonium for induction; and pentazocine, nitrous oxide, halothane, with or without pancuronium for maintenance of anaesthesia was used. Immediately after the surgery 75rng diclofenac sodium was given intravenously over 15 minutes as a bolus dose and then its infusion at 6.26 mg per hour was continuously run for 48 hours. In spite of the continuous infusion, if pain persistently remained above 5 on VAS, rescue analgesia was provided with 25mg (1 ml) diclofenac sodium 1/V. 50% of patients remained almost pain free on I/V infusion of diclofenac sodium and rescue analgesia was never required in them. Patients given rescue analgesia once were 12 (24%) and requiring it twice were 7(14%). Only in 6 patients rescue analgesia was given more than twice *(50mg).* The effect of intravenous water based diclofenac sodium on vital signs, laboratory values regarding coagulation, hepatotoxicity. nephrotoxicity and clinical side effects were monitored throughout the study period. No Significant adverse effects were noted.

RESULTS: In 88% cases intravenous diclofenac was proven effective in controlling postoperative pain.

CONCLUSION: The results showed that intravenous diclofenac sodium is an effective and safe drug for the postoperative pain management.

INTRODUCTION

Humanitarian concern for the patients requires that the anaesthesiologists should ensure the provision of good analgesia, not only intra-operatively, but also in the post operative period.

The traditional management of postoperative pain comprises of the prescription of a standard dose of an analgesic, to be given parenterally on demand by a paramedical staff when the patients' pain exceeds the threshold. However, most of the patients report dissatisfaction with the quality of postoperative analgesia. Most commonly opioids are used which cause ventilatory depression, urinary retention, nausea and vomiting to a variable degree.

With more understanding of the role of inflammatory mediators in the genesis of pain at the site of surgery, the use of NSAIDs has become increasingly popular over the past few years. Every route of administration has been employed in case of these drugs, and may be given orally, rectally, intramuscularly or intravenously (diclofenac, ketorolac). NSAIDs have been shown to be effective analgesics when administered after surgery as judged by either a reduction in pain scores and or by an opioid sparing effect.

PURPOSE

This prospective randomized single blind trial was designed to evaluate the efficacy and establish the safety of use of intravenous diclofenac sodium for cost operative pain management.

PATIENTS AND METHODS

A prospective, randomized, single blind study consisting of 50 patients undergoing surgery under general anesthesia at Civil Hospital. Karachi.

INCLUSION CRITERIA

- Age above 15 years
- ASA I, II, III
- Elective surgeries
- Types of surgeries
  - General Surgery
  - Gynaecological & Obstetrical Surgery
  - Fasciomaxillary Surgery
  - Neurosurgery
  - Orthopedic Surgery
  - Urological Surgery
  - Plastic Surgery
  - Thoracic Surgery

EXCLUSION CRITERIA

- Ulceration of Gastrointestinal tract
- Allergy to NSAID's
- Bleeding disorders
- Renal insufficiency
- Bronchial asthma
- ASA IV and V

STUDY

Informed consent was taken. A standardized anaesthetic technique consisting of thiopentone 3-5 mg / kg intravenously and suxamethonium 1-1.5 mg / kg intravenously was used for induction and intubation. Halothane 1-2% in nitrous oxide 50% and oxygen 50% was used for maintenance of anaesthesia. Supplimentation with pentazocine 15-20 mg I/V with or without pancuronium 0.04mg/kg was needed in some of the patients.

Post-operatively, 75mg Diclofenac Sodium was given slowly over 15 min immediately after surgery and 6.2mg/hour (75mg diclofenac sodium in 1000ml 5% D/W or 0.9 saline drip) in the form of continuos I/V infusion for 48 hours was given continuously.

Patients were brought to surgical ICU post operatively. Blood pressure, pulse and respiratory rate were continuously monitored and recorded from pre-operative period to 48 hours of postoperative period. Analgesic effect was assessed by quantification of pain (pain scoring) by visual analogue scale, '0'. Score meaning no pain and '10' meaning severe pain.

During the whole period drug tolerance was also assessed clinically to establish safety. Blood samples for PT, APTT, SGPT and creatinine were taken twice, before surgery and the second one at the end of trial.

RESULTS

The results of this clinical trial are very encouraging regarding efficacy and safety of intravenous diclofenac sodium in postoperative pain management. Total number of cases selected randomly was fifty, out of them 35 were male and 15 were female. The largest group belonged to the third decade (32%).

Table 1: Demographics

Sex Distribution	No. of cases	Percentage
Male	35	70
Female	15	30
Age Distribution		
15-20	13	26
21-30	16	32
31-40	13	26
41-50	07	14
50+	01	02

Patients underwent a variety of surgical procedures. Table 2 summarizes the type of surgical procedures. Majority of the cases was of orthopaedic and general surgery (78%) groups.

Table 2: Type of Surgery.

	No. of cases	Percentage
Orthopaedic	20	40
General	19	38
Gyne-Obs	04	08
Urology	02	04
Fasciomaxillary	02	04
Plastic	01	02
Neurosurgery	01	02
Thoracic	01	02

Duration of surgery was between 30 to 180 minutes which clearly shows the degree of surgical trauma that the patients had to undergo.

Table 3: Duration of Surgery

	No. of cases	Percentage
30-60 minutes	15	30
60-90 minutes	23	46
90-120 minutes	08	16
more than 120 minutes	04	08

Quantification of pain was done according to visual analogue scoring ranging from 0 to 10, where 0 meant no pain, while 10 signified the severe most pain. In the

immediate postoperative phase most of the patients were under the influence of intra operative analgesia. By giving them intravenous diclofenac infusion in the postoperative period, their pain status remained well under control. Table 4 summarizes their pain scores according to VAS at different intervals,

Table 4: Pain status according to VAS

	0 hrs.	6 hrs.	12 hrs.	24 hrs.	48 hrs.
Mean	2.4	0.6	0.7	0.14	0.32
Median	7	3	3	1	1
Mode	0	0	0	0	0
Range	0-10	0-8	0-6	0-5	0-10

In 50% of cases, pain was effectively abated by diclofenac infusion. While 38% of cases required rescue analgesia with 25-50 mg diclofenac I/V stat during their 48 hours stay in the surgical ICU. 12% of cases needed rescue analgesia twice or more than 3 times i.e. 50mg or more. This shows intravenous use of diclofenac sodium for post operative pain management is very efficacious (88%). Table 5 depicts the frequency of rescue analgesia employment.

Table 5: Rescue Analgesia Requirement

No.of times	Total mg	No.ofcases	% of cases
0	0	25	50
1	25	12	24
2	50	07	14
3	75	04	08
4	100	01	02
5	125	0	0
6	150	01	02

Regarding safety, increases in prothrombin time of more than 3 seconds was noted in 8 cases. APTT increased in 7 cases. SGPT in 2 cases increased almost two folds. Serum creatinine in one case rose above normal value.

There was no clinical problem requiring active intervention, like oozing from surgical wound or bleeding in patients with raised PT and APTT. They were observed and monitored throughout their stay in the hospital. Patients were safely discharged from their wards without any intervention. Increase in SGPT and serum creatinine was minor, not causing any clinical problem.

Regarding the vital signs, there was no abnormal variation noted except relative bradycardia in 3 cases (6%), which neither caused any haemodynamic instability nor required any medical intervention.

Phlebitis was noted in 11 (22%) cases, nausea and or vomiting in 4 (8%) cases, epigastric pain in 2 (4%) cases, and rigors was noticed in only one case which was not attributable to diclofenac, as it subsided itself within one hour and on restarting diclofenac infusion rigors did not recur. Over all adverse effects were few, which mandates continuous monitoring, however the drug can be safely used via intravenous route.

Table 6: Tolerability - Adverse Effects

Event	No. of cases
Phlebitis	11
Nausea/vomiting	04
Epigastric Pain	02
Rigors	01
Allergic reactions	0
Relative bradycardia	03

DISCUSSION

The results of this prospective, randomized, single blind study prove the efficacy and safety of' intravenous diclofenac sodium. The patients were pain free throughout the post operative period as assessed by pain scoring by means of visual analogue scale.

Initial scoring of pain was also low because patients were already under the effect of intraoperative analgesics. They were given bolus dose of diclofenac sodium and then infusion of diclofenac 6.25 m/g hour started. Mean pain scoring immediately after surgery was 2.4 and then was below 1 in the next 48 hours. Patients were pain free in 25 cases(50%) without any rescue analgesia. Rescue analgesia was given in 19 cases upto 50mg. Only in 6 (12%) cases rescue analgesia more than 50mg was given.

Prothrombin time was raised in 8 cases (16%) and APTT was raised in 7 cases (14%). These patients were monitored in the ward throughout their stay in hospital but there were no clinical problems like oozing from surgical wound, which is known to be due to NSAID induced platelet dysfunction, which is reversible, and last about its elimination half life (24-46 hours.) This anti platelet affect does not appear to increase the incidence of post operative hemorrhage appreciably.

SGPT was raised in *2* (4%) cases and creatinine in I (2%) case without any clinical problem.

Regarding drug tolerance of diclofenac, phlebitis was noted in eleven cases, nausea / vomiting in four cases,

relative bradycardia in three cases and epigastria pain in two cases. These symptoms did not worsen with the continued usage of the diclofenac sodium infusion.

CONCLUSION

It can be concluded that intravenous diclofenac sodium can be safely used for effective post operative pain management without side effects of any serious concern.

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NEW PRODUCTS

PYROLATE.

At last glycopyrrolate has been launched in Pakistan. An anticholinergic claimed to be superior to atropine in that it is longer acting and does not cross blood brain barrier. Antivagal effects persist for 2-3 hours and anti-sialagogue effect last for upto 7 hours. It is indicated as antimuscarinic anti-arrhthmic agent. Dose for pre-medication is 4.4 μg/kg body wt half to one hour before induction of anaesthesia. 0.2 mg is added to each mg of neostigmine (0.5 mg per 2.5mg of neostigmine as reversal agent.

Supplied as 1ml ampoules containing 0.1 mg glycopyrrolate USP.

Marketed by: **Brookes Pharmaceutical Labs.**

LIOMETACEN

Liometacen (Meglumine Indomethacinate is a potent analgesic with antipyretic and anti-inflammatory activity. Liometacen allows a prompt relief of pain, fever and inflammation, being most suitable for treating particularly severe conditions.

Pain syndromes, biliary and renal colic's, post-operative pain, cancer pain, chronic pain, rheumatoid arthritis, musculoskeletal pain syndromes, post-traumatic pain & sport injuries.

The recommended starting dosage is 1 ampoule of LIOMETACEN every 12 hours. In chronic cases, depending on the time-course of the disease, one ampoule of Liometacen should be injected either daily or every other day. LIOMETACEN can be given by direct intravenous route, dissolving 1 ampoule in 5ml saline solution and injecting very slowly in 3-5 minutes.It can be given intra-articularly, dissolving 1 ampoule in 2ml of 2% procaine or mepivacaine solution, then infiltrating it into the articular cavity or into the tendon after aspiration of any liquid possibly present.

Marketed by: **Chiesi Pharmaceuticals (Pvt) Ltd.**

LESCOL

A brand of fluvastatin sodium, LESCOL has been introduced in the local market as anti-hypercholestrolaemic agent. It has been shown to have comparable effects with simvastatin on serum liquid but shows fewer adverse events and smaller increases in hepatic / cardiac enzymes levels than simvastatin. It reduces LDL-C by 25%-45%. It also retards the progression of existing atherosclerotic lesions as well as producing plaque stabilisation. It is presented as capsules containing 20mg fluvastatin sodium, and 40mg fluvastatin.

Marketed by: **Novartis, 16-West Wharf, Karachi.**

CALMIN 600

It is a balance I.V. nutritional solution containing a logical combination of amino acids, vitamins, carbohydrates and electrolytes. It provides 600 calories in one-liter solution. It is ideally suited for parentral nutrition in following conditions. Gastrointestinal impairment, which may arise in conditions like anorexia, short bowel syndrome and severe gastrointestinal disorders. To meet increased metabolic demand in cases of severe burns, trauma and post surgery. Critical cases requiring exogenous nutrition such as tumor, severe infection, severe stress and protein deficiency. Usual dose is of 500ml of CALMIN 600 to be infused over 4-6 hours at the rate of 20-30 drops/minute.

Supplied as 500ml in glass bottle.

Marketed by: **SAMI Pharmaceuticals (Pvt) Ltd. Karachi.**