Clinical Investigation

Effect of pre-operative rectal diclofenac suppository on post-operative analgesic requirement in cleft palate repair: A randomised clinical trial

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ABSTRACT

Background: Opioid analgesics used for analgesia are associated with sedation, respiratory depression and post-operative nausea and vomiting. Non-steroidal anti-inflammatory drugs such as diclofenac are a safe and effective alternative with opioid-sparing effect. **Objective:** To evaluate the effectiveness of pre-operative rectal diclofenac suppository (1 mg/kg) in cleft palate repair for post-operative analgesia and reduction in post-operative opioid requirements. **Study Design:** A randomized clinical trial. **Methods:** After obtaining approval from the institutional ethical committee, 60 children were allocated by a computer-generated randomisation into two groups of 30 each; group D (Diclofenac group) and group C (Conventional group). Children in group D and group C were similar in all aspects except for the fact that group D children received 1 mg/kg diclofenac suppository after induction. Pain was evaluated using modification of the objective pain scale by Hannallah and colleagues for 6 h post-operatively by an anaesthesiology resident or nursing staff who was blinded to the group. If the pain score was more than 3, rescue analgesic I.V. fentanyl 0.5 μgm/kg was administered. The pain scores at different intervals, number of doses and quantity of rescue analgesic required were noted. **Results:** We observed that pre-operative rectal diclofenac provided effective analgesia in the immediate post-operative period, as evidenced by reduced pain scores and reduced opioid requirement (P=0.00002). There was no evidence of any increased perioperative bleeding in the diclofenac group. **Conclusion:** Pre-operative rectal diclofenac reduces opioid consumption and provides good post-operative analgesia.

Key words: Cleft palate repair, preemptive analgesia, rectal diclofenac

INTRODUCTION

Pain in children is a complex phenomenon, as it is difficult to differentiate crying or restlessness due to pain from that of hunger or fear. Pain triggers complex biochemical and physiological stress responses and induces impairment in pulmonary, cardiovascular, neuroendocrinal, gastrointestinal, immunological and metabolic functions.[1]

Cleft lip-palate is one of the most common congenital anomaly requiring surgical intervention at a very early stage in life. The incidence is reported to be one in 897 live births.[2] Opioids have been the mainstay of post-operative pain relief but, recently, non-opioids are being considered because of the high incidence of nausea, vomiting and also concerns about the respiratory depression and sedation seen with opioids.

Diclofenac sodium is an effective and safe analgesic in children and, when given pre-operatively, has shown to provide preemptive analgesia.[3-5] Rectal diclofenac suppositories are available and are proved to be safe for use in children.[6]

The present study was carried out to evaluate the effect of pre-operative rectal diclofenac suppository (1 mg/kg) on post-operative analgesic requirement and

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to determine the reduction in opioid requirement in the immediate post-operative period.

METHODS

This study was conducted during December 2006 to January 2008. After obtaining the Institutional Ethical Committee clearance and informed consent, 60 ASA grade 1 children aged between 9 months (mths) and 7 years (yrs) posted for cleft palate repair were enrolled in the study. Taking Zα=1.65, Zβ=0.84 and power=80%, a sample size of 10 in each group was arrived at. However, in our study, a sample size of 60 (30 in each group) was taken to achieve more than 80% power of study.

Exclusion criteria for enrollment in the study were ASA grade 2 and above, prolonged bleeding time/clotting time, history suggestive of kidney or liver disease, history suggestive of allergy to aspirin/related drugs, history suggestive of bleeding disorders/asthma/anorectal anomaly and treatment with other analgesics/anticonvulsants/anticoagulant.

All children were kept nil by mouth for at least 4 h prior to surgery. The children were then allocated into group D (Diclofenac suppository group) or group C (Conventional group) according to a computer-generated randomisation table. They were premedicated with intramuscular inj. glycopyrrolate 0.005 mg/kg and inj. ketamine 5 mg/kg in the pre-operative waiting room and shifted to the operating room after adequate sedation. In the operating room, children were oxygenated with 100% oxygen with Jackson Rees modification of Ayres "T" piece. Meanwhile, an appropriate-sized intravenous line was secured and standard monitors were attached. The children were induced with intravenous (I.V.) ketamine 1 mg/kg and intubation was facilitated with I.V. suxamethonium 1–2 mg/kg. Intubation with an appropriate-sized uncuffed Ring-Adair-Elwyn (RAE) orotracheal tube (South Pole tube) was done and a throat pack was placed. Rectal diclofenac suppository (1 mg/kg) was inserted in lateral position following induction and intubation in group D children, while children belonging to group C received no suppository. The time of insertion of the suppository was noted.

General anaesthesia was maintained in both the groups via a closed circuit with 50% oxygen in nitrous oxide along with I.V. fentanyl 1 μgm/kg, I.V. midazolam 0.05 mg/kg and I.V. vecuronium 0.1 mg/kg. Palate repair in all the patients was by the Veau–Wardill–Kilner technique. Intra-operatively, continuous monitoring of pulse rate (PR), arterial oxygen saturation (SpO2), temperature, end tidal CO_2 ($EtCO_2$) and blood pressure (BP) was done and any bleeding in excess of usual was noted. All children received I.V. Isolyte P as per standardized calculation. At the end of the surgery, adequate reversal was done with I.V. glycopyrrolate 0.01 mg/kg and I.V. neostigmine 0.05 mg/kg. Haemostasis was inspected for and the throat pack was removed. Extubation was done after thorough oral suctioning.

Post-operatively, in the recovery room, all the patients were monitored for haemodynamic parameters (PR, SpO_2 and BP) every 15 min for the first 90 min, followed by every hour up to 6 h post-operative. Pain was assessed by an anaesthesiology resident and nurse trained to use the Modification of Objective pain scale by Hannallah and colleagues [Table 1] in the recovery room.[7] The person assessing the pain was blinded to the study group. Intravenous fentanyl 0.5 μgm/kg as rescue analgesic was administered if the pain score was more than 3.

The number and total dose of rescue analgesic (i.e. I.V. fentanyl 0.5 μgm/kg) required was noted. Observation for any bleeding in excess of usual was noted.

RESULTS

All the data collected were tabulated in terms of mean and standard deviation (SD). The data were compared between the groups in the following manner: age, weight and duration of surgery were compared using the Unpaired Student's t test. Non-parametric Mann Whitney U test was used for comparing the mean (SD) pain scores at different intervals. Comparison of number of children requiring rescue analgesic was

Table 1: Pain scoring (modification of the objective pain scale by Hannallah and colleagues)

Observation	Criteria	Points
Crying	No crying	0
	Crying but responds to TLC	1
	Crying not responding to TLC	2
Movement	None	0
	Restlessness	1
	Thrashing	2
Agitation	Asleep/calm	0
	Mild	1
	Hysterical	2

TLC - Tender loving care; Pain defined by pain score >3 points, rescue analgesia required

done using the Chi-Square test. The comparison of total dose of fentanyl consumed (microgram, μgm) was done using Unpaired Student's t test.

$P<0.05$ was considered as statistically significant (S).

The age, weight, sex ratio and duration of surgery were comparable in both the groups [Table 2].

There was no significant difference in mean pain scores at 0 min and 30 min in the post-operative period between both the groups. However, a significant difference in mean pain scores was observed at 60 min and 90 min. Mean pain scores were comparable between the groups at 2, 3, 4, 5 and 6 h post operatively [Figure 1], [Table 3].

Only eight cases (26.66%) in group D required rescue analgesic (I.V. fentanyl) as compared with 24 cases (80%) in group C in the post-operative period of 6 hours. There was a highly significant decrease in the number of children requiring rescue analgesic ($P=0.0001$) in group D [Table 4]. *P*-value by Chi Square test=0.0001 (S).

Duration of adequate post-operative analgesia, taken from the completion of surgery till the pain score was more than 3, could not be assessed as the study was restricted for a follow-up period of 6 h post-operatively.

There was a statistically significant reduced consumption of fentanyl 1.67±3.30 μgm in the diclofenac group ($P=0.00002$) compared with the conventional group in which it was 6.08±4.03 μgm.

Five of the 24 children in group C received a second dose of rescue analgesic as compared with group D, where no child required a second dose of rescue analgesic [Table 5].

Other observations, like perioperative bleeding in excess of usual, were not evident in any child receiving diclofenac.

DISCUSSION

The multimodal armamentarium to cater to the analgesic needs of the child includes non-steroidal anti-inflammatory drugs (NSAIDs) tailored to suit the individual needs of children. NSAIDs have become increasingly popular in the perioperative management of pain. In general, NSAIDs have been shown to be effective analgesics, as judged by either a reduction in pain scores and/or opioid sparing effect.[8,9] The pharmacokinetic and pharmacodynamic properties

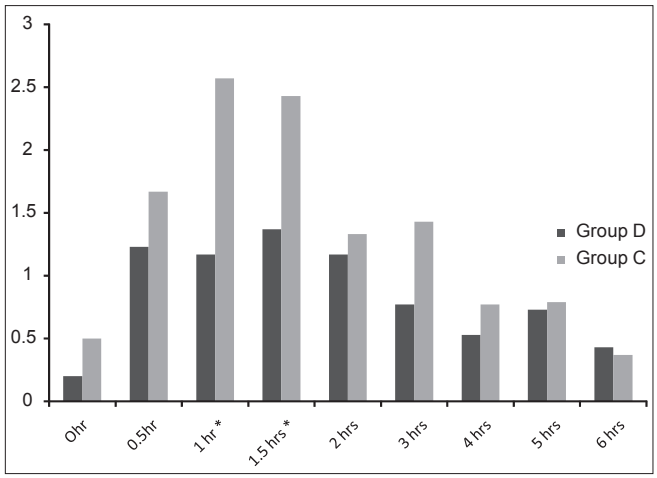

Figure 1: Mean pain scores in both the groups at different time intervals. **P* value significant at 1 and 1.5 h

Table 2: Age, weight and sex distribution in both the groups

Character	Diclofenac group Mean±SD	Conventional group Mean±SD
Age (months)	33.60±20.71	27.13±17.18
Weight (kg)	10.31±3.07	9.72±2.67
Male:Female	20:10	15:15

Table 3: Mean±SD pain scores at different time intervals in both the groups

Time	Group D Mean±SD	Group C Mean±SD	Mann Whitney U test
0 min	0.2±0.41	0.5±0.78	0.2143 (NS)
30 min	1.23±1.01	1.67±1.54	0.4464 (NS)
60 min	1.17±0.99	2.57±1.79	0.0036 (S)
90 min	1.37±1.35	2.43±1.52	0.0064 (S)
2 h	1.17±1.23	1.33±1.12	0.4598 (NS)
3 h	0.77±0.94	1.43±1.33	0.0519 (NS)
4 h	0.53±0.68	0.77±0.68	0.1958 (NS)
5 h	0.73±0.98	0.79±0.82	0.6009 (NS)
6 h	0.43±0.68	0.37±0.56	0.8825 (NS)

Table 4: Number of cases requiring rescue analgesics in both the groups

	Rescue analgesic		
Group	Yes	No	Total
Diclofenac	8 (26.66)	22 (73.33)	30
Conventional	24 (80.00)	6 (20.00)	30
	32	28	

Figures in parenthesis are in percentage

Table 5: Number of rescue analgesic doses required in both the groups

No. of doses	Diclofenac group	Conventional group
0	22 (73.33)	6 (20)
1	8 (26.66)	19 (63.33)
2	0	5 (16.66)

Figures in parenthesis are in percentage

of diclofenac and nociceptor modulation necessitate their administration in advance of the anticipated time of analgesic requirement, pre-emptively.[5]

Pre-emptive analgesia is defined as an antinociceptive treatment that prevents establishment of altered central processing of afferent input from injuries.[10] Diclofenac administered rectally is a safe and a convenient approach resulting in complete absorption and sustained release of drug providing early onset and long duration of post-operative analgesia. Diclofenac is safe in children above 6 months of age, like other NSAIDs.[11,12]

In our study, we have used the 12.5 and 25 mg suppositories at a dose of 1 mg/kg. The larger suppositories were divided or, in the case of the smaller suppositories, more than one were placed to meet the 1 mg/kg dosage. Division of suppository for adequate dosing was done. This was based on the assumption that as per quality standards U.S. Pharmacopoeia (USP30-NF25), content/drug uniformity has to be ensured in a suppository.[13] Further, the suppositories were divided vertically instead of horizontal to minimize the effect of non-uniform distribution of drug for adequate dosing.

The rectal suppository that is absorbed in 30–60 min and achieves T_{max} after 50 min of insertion offers a simple maneuver to administer the drug, equaling the analgesic efficacy of the oral preparation.[14] In the process, it bypasses the enteric system, where the danger of any NSAID lurks.

Previous studies using rectal diclofenac convinced us to choose a rectal diclofenac dose of 1 mg/kg, although it is less when compared with few other studies.[15] A recent metaanalysis on diclofenac dose recommendation for surgical pain in children aged 1–12 years recommends 0.5 mg/kg for rectal diclofenac.[16] In most other studies, children received a second dose of diclofenac after a period ranging from 8 to 12 h from the first dose. We however restricted our study to a single 1 mg/kg dosage after induction as our primary objective was to study the reduction of opioid consumption in the immediate post-operative period, i.e. 6 hours. Beyond 6 h, children would be expected to be awake, and repeating a suppository may be difficult. Also, after 6 h, oral analgesics may be better accepted and preferred. The time of insertion of suppository was just after induction and intubation with a pre-emptive motive. Until the drug achieved T_{max} by 50 min, intra-operative analgesia was provided with inj Fentanyl. The use of placebo suppository was not included in the study design as diclofenac suppositories were placed after induction.

On comparing the pain scores between the two groups in our study, there was no statistically significant difference between the two groups for the first 30 min. This can be attributed to the residual effect of intra-operative analgesic (I.V. fentanyl 1 μgm/kg). At 60 and 90 min, there was a significant reduction in pain scores in group D as compared with group C. This can be attributed to the analgesic action of diclofenac. At 2, 3, 4, 5 and 6 h, there was no significant reduction in pain scores in group D as compared with group C. This may be attributed to a significant majority of children (up to 50%) in group C receiving rescue analgesic by 4 h post-operatively. Hence, they were subsequently pain free and did not have pain scores of more than 3.

It was observed that rectal diclofenac (1 mg/kg) was effective from 30 min post-operatively and extended to cover a period of up to 6 h, as evidenced by the reduced pain scores. It can be further assumed that the analgesic action extended beyond 6 h, although a systematic assessment of pain was not carried out during this period. This observation is supported by previous studies by Bone ME and Fell D, who reported a duration of analgesia for 7.3 h.[17] Few other studies have reported duration of analgesia extending up to a period of 12.45 and 14 h.[18,19]

There was a significant reduction in the number of children receiving rescue analgesic in group D. Five children in group C received rescue analgesic twice in a period of 6 h. On comparing the quantity of I.V. fentanyl consumed in both groups, the reduction in fentanyl consumption in group D was highly significant. Our study showed that pre-operative rectal diclofenac significantly reduces the number of doses and the quantity of opioid required in the post-operative period. Our observation is also supported by previous studies by Moffat AC and colleagues, who demonstrated a morphine-sparing effect of diclofenac in upper abdominal surgeries.[20] Other studies have also demonstrated a 30% reduction in post-operative opioid consumption.[21,22]

The children were also observed for perioperative blood loss. It was found that there was no significant bleeding in excess of usual in group D as assessed by the operating and recovery personnel. This observation is in concurrence with the conclusion

drawn by the Cochrane review on safety of diclofenac in the paediatric age group.[4]

CONCLUSION

Rectal diclofenac sodium is suited for a pre-emptive approach and proves to be an efficient drug as part of balanced analgesia and helps to reduce consumption of opioids in the post-operative period.

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Announcement

BEST TEACHER AWARD

The Editorial Board of Indian Journal of Anaesthesia (IJA) is happy to learn that our member, Dr. A. L. Meenakshi Sundaram is honoured with the "Best Teacher Award" by the Tamil Nadu Dr. MGR Medical University, Chennai in recognition of his contributions to the cause of Medical Education.

The Editorial Board wishes Dr. Meenakshi Sundaram with many more such awards & encourage him to serve the humanity for many more years.

Dr. S S Harsoor
Editor, Indian Journal of Anaesthesia (IJA)