Asian Journal of Medicine and Health

Volume 22, Issue 8, Page 124-133, 2024; Article no.AJMAH.120386
ISSN: 2456-8414

Effect of Two Regimens of Rectal Diclofenac on Post Adenotonsillectomy Pain in Children

Chinedu Paul Iwuoha [a++], Alfred Tamunoigbanibo Aggo [a*] and Uyoata Udo Johnson [a]

[a] *Department of Anaesthesia, Paediatric Anaesthesia Unit, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria.*

Authors' contributions

This work was carried out in collaboration among all authors. Author CPI did the data acquisition, interpretation and initial intellectual content development. Author ATA did the initial study conception, designed the study, prepared the manuscript and did final intellectual content development. Author UUJ approved the final version, integrity appraisal and reviewed the manuscript critically. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajmah/2024/v22i81077

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/120386

Original Research Article

Received: 24/05/2024
Accepted: 26/07/2024
Published: 02/08/2024

ABSTRACT

Aim: To determine the post adenotonsillectomy analgesic effect of single versus divided dose regimen of rectal diclofenac in children.
Study Design: Prospective, randomized, double blind, comparative study.
Place and Duration of Study: University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria, from June to November, 2023.

[++] *Consultant;*
**Corresponding author: E-mail: alfred.aggo@uniport.edu.ng;*

Cite as: *Iwuoha, Chinedu Paul, Alfred Tamunoigbanibo Aggo, and Uyoata Udo Johnson. 2024. "Effect of Two Regimens of Rectal Diclofenac on Post Adenotonsillectomy Pain in Children". Asian Journal of Medicine and Health 22 (8):124-33. https://doi.org/10.9734/ajmah/2024/v22i81077.*

Methodology: Following ethical approval (Ethical reference UPTH/ADM/90/S.II/VOL.XI/1285, granted 25th November, 2021) and parental consent, 50 children, of American Society of Anesthesiologists (ASA) class I and II, aged 1 – 6 years, were randomized into groups I and II, of 25 each. All children had intratracheal general anaesthesia induced with propofol, followed by atracurium, fentanyl, and maintained by isoflurane in 100% Oxygen. Group I received suppository diclofenac 2 - 3mg/kg rectally, in two divided doses 12 hours apart (first dose at induction), while group II received suppository diclofenac 2 - 3mg/kg rectally, as single dose (at induction). Pain was assessed using the Face, Leg, Arm, Cry, Consolability (FLACC) scale. The time to first analgesic request, (TTFAR) was defined as the period from rectal drug administration to pain score of ≥ 4. Analgesic was given when FLACC score was ≥ 4.

Results: All 50 subjects completed the study. The mean TTFAR (hours) was significantly more prolonged (7.82±1.18) in group I compared to 5.42±1.19 observed in group II, P = 0.0081, with significantly greater 24-hour analgesic consumption in group II, P = 0.0044, and 0.0003.

Conclusion: Suppository diclofenac administered rectally in two divided doses achieved significantly more prolonged postoperative analgesia compared to single equivalent dose.

Keywords: Rectal diclofenac; single full dose; divided dose.

1. INTRODUCTION

Adenotonsillectomy ranks as one of the common surgical procedures in children, that is associated with significant pain posing a major concern, especially in the first 24 hours [1]. In the United States, more than 500,000 adenotonsillectomies are done annually in children <15 years of age. In Nigeria, data from various centres revealed 310 adenotonsillectomies were performed from 2018 to 2022 in Enugu, 115 cases in 2021 to 2022 in Lagos, and 75 cases in 2022 at Port Harcourt Teaching Hospital [1,2]. About 67% of children experience moderate to severe post adenotonsillectomy pain [3]; this has been attributed to inadequate knowledge in preemptive pain management strategies, inconsistencies in pain assessment procedures, absence of analgesic regimens that account for inter-individual differences and requirements, and the misconception that children, especially infants, do not experience pain [3]. Besides, young children, due to age-related developmental, cognitive and emotional variations, have difficulty in comprehending and estimating such a subjective experience as pain [4]. Poorly treated postoperative pain can orchestrate numerous deleterious effects: acute neurohumoral changes and neuronal remodeling result in persistent chronic pain states; psychologically, the consequences of pain on both the child and the parent such as anxiety, fear and sleep disturbances trigger long-lasting emotional distress [5]; ineffective coughing leading to retention of secretions predisposes to atelectasis and pulmonary infection, while catecholamine release, owing to sympathetic upheaval, induce decreased gut motility resulting in paralytic ileus [5,6].

2. MATERIALS AND METHODS

Institutional approval was secured from the University of Port Harcourt Teaching Hospital for a prospective, randomized, comparative, double blind study. All 50 subjects completed the study which was conducted from June to November, 2023, in the Otorhinolaryngology (ORL) theatre, recovery room and ward, in the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria. Codes were kept by the Nurse in the ORL surgical ward in conjunction with the second Research Assistant for gaining rapid access to every subject, if adverse effects occurred.

All subjects had preoperative evaluation and preparation the day before surgery; the parents withheld solid food 6 hours, breast milk 4 hours but gave clear glucose fluid till 2 hours prior to surgery. The inclusion criteria comprised children aged 1 – 6 years, weighing 10 – 20 kg, scheduled for elective adenotonsillectomy, belonging to ASA class I or II and whose parents gave consent, while parental decline to consent for study, respiratory tract infection, ASA > II, age < 1 year or > 6 years, weight < 10kg or > 20kg, clotting derangement, history of kidney/liver disease, asthma, haemoglobinopathy and anorectal inflammatory lesion constituted the exclusion criteria.

2.1 Sample Size Determination

The sample size (n) was calculated using the formula for comparison of means [7].

$$n = \frac{(Z\alpha + Z_\beta)^2 \times (SD_1^2 + SD_2^2)}{(\mu_1 - \mu_2)^2}$$

$Z\alpha$ =1.28, with power of 90% in this study; Z_β = 1.96, using 5% significance level.

SD_1 = standard deviation of group 1 and SD_2 = standard deviation of group 2.

The standard deviation of the group that received single dose rectal diclofenac was 1.56 in a related study [8]. Based on the null hypothesis, the standard deviations for the single dose and divided dose rectal diclofenac groups, it was assumed, were not different; hence, $SD_1 = SD_2 = 1.56$

$\mu_1 - \mu_2$ = the expected difference in hours of the duration of effective analgesia between the two groups, and for this study, it was 1.5 hours.

Substituting, $n = \frac{(1.28 + 1.96)^2 \times (1.56^2 + 1.56^2)}{1.5^2}$

$= 22.7084$.

Adding 10% for attrition, each group required 25 subjects; therefore, a total of 50 patients were recruited for the study.

Patients categorisation into groups I and II by simple random sampling, as well as blinding, were ensured through recruitment of Research Assistants. The parents of the children picked from a bag containing 50 sealed opaque envelopes concealing equal ratio of slips labelled group I and group II, under the supervision of the first Research Assistant and the Nurse in the Theatre Reception; the envelope picked was excluded from the bag and the subject automatically assigned to the group designated. The second Assistant who was blinded to the outcome of the study, prepared and administered the study drugs according to the subjects' groups and weight specifications. Group I received suppository diclofenac 2 - 3mg/kg rectally, in two divided doses 12 hours apart (first dose at induction), while group II received 2 - 3mg/kg rectally, of same suppository diclofenac as single full dose (at induction). Subjects weighing 10 to 12kg received 25mg, and those weighing 17 to 20kg received 50mg diclofenac, either as a single dose or in divided doses. For the avoidance of splitting of the diclofenac suppository, children weighing 13 to 16kg in group II received 37.5mg (25mg and 12.5mg suppositories) as a single dose while the subjects in same weight range in group I received 25mg diclofenac as initial dose, then 12.5mg 12 hours later.

On the morning of surgery, 30 minutes prior to induction, subjects were premedicated with apple juice-flavoured midazolam 0.5mg/kg orally for separation anxiolysis. Multiparameter monitor (MEC 1000 Mindray, United Kingdom) was attached along with a precordial stethoscope for baseline recording and continuous mornitoring of heart rate (HR), non-invasive blood pressure (NIBP), temperature and peripheral arterial haemoglobin oxygen saturation (SpO_2).

All patients had general anaesthesia and tracheal intubation, facilitated by intravenous propofol 2mg/kg, followed by atracurium 0.5mg/kg, fentanyl 2ug/kg, and maintained with Isoflurane 1 – 1.5% in 100% Oxygen via a Mapleson F breathing system. Immediately after tracheal intubation, the first dose of suppository diclofenac (VOLTAREN, Novartis Pharmaceuticals UK Limited) was inserted to a depth of 1.5 – 2 cm, using the little finger lubricated with a water-based jelly (K-Y Jelly, IDS Manufacturing Ltd., Thailand). The Principal Researcher who was blinded to the group allocation and study drug preparation/administration, monitored and recorded the patients' intra-operative parameters. All children received intravenous lactated Ringer's solution perioperatively according to the 4-2-1 rule.

The following parameters were monitored intra-operatively: HR and NIBP [systolic (SBP), diastolic (DBP), mean arterial (MAP)] every 5 minutes till the end of surgery; SpO_2 to ensure a value >95%; peripheral temperature to maintain normothermia (36.5 - 37.4ºC); blood loss by visual estimation, and intravenous fluid administration.

At the end of surgery, the orohypopharynx of every patient was suctioned under direct vision, isoflurane was discontinued, and residual muscle paralysis was reversed using intravenous 0.025mg/kg atropine and 0.05mg/kg neostigmine. Following tracheal extubation subjects were shifted to the recovery room where, for 1 hour, SpO_2, respiratory rate (RR), HR, SBP, DBP, MAP and temperature were assessed every 15 minutes, and pain every 30 minutes using FLACC scale [9], before transfer to the ward. Pain was then assessed at 2, 4, 6, 12, and 24 hours. At a FLACC score of ≥ 4, intravenous fentanyl 0.5 µg/kg, and acetaminophen 15mg/kg 6 hourly, were administered and repeated as required. Subjects were also evaluated for the occurrence of any adverse effects.

2.2 Data Collection and Analysis

Data were entered into Excel spreadsheet and exported to the Statistical Product and Service Solutions (SPSS) version 20.0 (Armonk, NY: IBM Corp.) for statistical analysis by a Statistician not involved in the study. Statistical significance was set at $p < 0.05$.

3. RESULTS

A total of 50 children were recruited, and all completed the study. The demographic characteristics, ASA classifications and weights of participants in the two groups were comparable, with mean age (years) and mean weight (kg) of 3.12±1.62 versus 2.84±1.49, *P* = 0.527 and 14.44±2.87 versus 13.76±3.13, *P* = 0.427, respectively (Table 1).

The recorded baseline and 5 – 45 minutes intraoperative mean values correspondingly, were as well comparable in MAP (*P* = 0.303 and 0.929), SpO_2 (*P* = 0.077 and 0.155) and temperature (*P* = 0.83 and 0.918) across the groups **(**Table 2).

Again, group I and group II recorded statistically similar values in the mean duration (minutes) of surgery and anaesthesia, and estimated blood loss (ml), with corresponding *P* values of 0.341, 0.159 and 0.268 (Table 3).

Postoperatively, the Recovery room baseline median pain score was zero (0) in the two groups, with an interquartile range (IQR) from 0 to 0, p = 0.153; pain scores were also statistically similar at 15 to 60 minutes (*P* = 1.000), as well as at the 2nd and 4th hour, with corresponding *P* values of 0.195 and 0.176. However, from the 6th to the 24th hour pain scores became significantly lower in group I relative to group II, with the median IQR values of 2 (0 - 3) versus 4 (1 – 5) at the 6th, 1 (0 – 4) versus 4 (2 - 5) at the 12th, and 1 (1 - 2) versus 4 (1 - 5) at the 24th hour, with *P* = 0.046, 0.001, and 0.001 respectively. A 2nd to 24th hour postoperative period intergroup analysis showed an overall lower median and IQR values of 2 (0 - 3) versus 3 (0 - 4) respectively for group I and group II, the difference being statistically significant, p = 0.001 (Table 4).

Table 1. Subjects' demographics and ASA classification

Variables	**Group I n=25**	**Group II n=25**	χ^2***/t-test***	***P***
	Freq (%)	**Freq (%)**		
Age (years)				
1	4 (16.0)	3 (12.0)	5.99	0.308
2	6 (24.0)	12 (48.0)		
3	7 (28.0)	2 (8.0)		
4	2 (8.0)	4 (16.0)		
5	3 (12.0)	2 (8.0)		
6	3 (12.0)	2 (8.0)		
Mean (SD) [Range]	3.12±1.62 *[1-6]*	2.84±1.49 *[1-6]*	0.64^{α}	0.527
Sex				
Male	15 (60.0)	10 (40.0)	2.0	0.157
Female	10 (40.0)	15 (60.0)		
ASA				
I	24 (96.0)	22 (88.0)	1.09	0.297
II	1 (4.0)	3 (12.0)		
Weight (kg)				
Mean (SD) [Range]	14.44±2.87*[10-20]*	13.76±3.13*[10-20]*	0.80	0.427

χ^2 = Chi-Square, α=Student t-test

Table 2. Baseline and intra-operative vital parameters in the two groups

Variables	Group I n=25	Group II n=25	*t-test*	*P*
	Mean ± SD	Mean ± SD		
SBP (mmHg)				
Baseline	100.68±9.29	110.20±6.46	4.21	**0.0001***
5-45 minutes	106.76±3.55	111.91±5.56	3.90	**0.0003***
DBP (mmHg)				
Baseline	55.88±8.92	59.80±13.20	1.23	0.225
5-45 minutes	55.33±3.95	60.72±8.66	2.83	**0.0067***
MAP (mmHg)				
Baseline	70.0±7.95	68.08±4.68	1.04	0.303
5-45 minutes	67.52±5.73	67.64±3.42	0.09	0.929
PR/HR (b/min)				
Baseline	108.80±9.73	117.28±10.17	3.01	**0.0042***
5-45 minutes	117.31±31.67	115.23±8.85	0.32	0.752
SpO_2				
Baseline	99.12±0.33	99.0±0.00	1.81	0.077
5-45 minutes	99.0±0.00	99.07±0.25	1.44	0.155
Temperature (ºC)				
Baseline	36.93±0.14	36.97±0.21	0.88	0.383
5-45 minutes	36.94±0.13	36.95±0.15	0.10	0.918

**Statistically significant; t-test=Student t-test*

Table 3. Duration of surgery, anaesthesia and estimated blood loss

Variables	Group I n=25	Group II n=25	*T-test*	*P*
	Mean ± SD	Mean ± SD		
Duration of Surgery (*Minutes*)	36.60±4.26	35.40±4.55	0.96	0.341
Duration of Anaesthesia (*Minutes*)	39.40±3.91	41.48±7.24	1.26	0.159
Estimated Blood Loss (Ml)	66.40±19.34	60.0±21.02	1.12	0.268

T-test=Student t-test

Table 4. Postoperative FLACC pain scores at different time points

Time	Group I n = 25	Group II n = 25	*P*
	Median (IQR)	Median (IQR)	
Baseline	0 (0-0)	0 (0-0)	0.153
15 – 60 minutes	1 (0-1)	1 (0-1)	1.000
2 hours	2 (0 - 3)	3 (0 - 3)	0.195
4 hours	2 (0 - 3)	3 (0 - 3)	0.176
6 hours	2 (0 - 3)	4 (1 - 5)	**0.046***
12 hours	1 (0 - 4)	4 (2 - 5)	**0.001***
24 hours	1 (1 - 2)	4 (1 - 5)	**0.001***
2nd – 24th hour	2 (0 - 3)	3 (0 - 4)	**0.001***

*Data are expressed in median and interquartile range (IQR); *Statistically significant*

The mean duration (hours) of effective analgesia (described as the time to first analgesic request or pain score ≥4) experienced by participants, was significantly more prolonged (7.82±1.18) in group I relative to 5.42±1.19 observed in group II, with a p-value of 0.0081. Also, the total postoperative analgesic consumption in the groups within the first 24 hours was significantly greater in group II compared to group I, recording 15.52±4.06 versus 12.44±3.28 µg of fentanyl, *P* = 0.0044, and 263.04±84.32 versus 186.60±47.65 mg of acetaminophen, *P* = 0.0003, respectively. Although the mean time (hours) to first oral intake was slightly higher (4.72±1.51) in group II, in comparison to 4.24±1.85 as was observed in group I, the difference was not significant, *P* = 0.3212 (Table 5).

There was no occurrence of postoperative bleeding, vomiting or fever in any of the children in the two groups of this study (Table 6).

Table 5. Time to first analgesic request (TTFAR), 24-hour total analgesic consumption, and time to first oral intake (TTFOI) in the groups

Variable	Group I n = 25	Group II n = 25	Mann-Whitney	*T-test*	*P*
Time to first analgesic request (hours)	7.82±1.18	5.42±1.19	10.08		**0.0081***
24-hour total analgesic consumption	12.44±3.28	15.52±4.06		2.99	**0.0044***
Fentanyl (µg)	186.60±47.65	263.04±84.32		3.95	**0.0003***
Acetaminophen (mg)					
Time to first oral intake (hours)	4.24±1.85	4.72±1.51		1.00	**0.3212**

**Data are expressed as Mean±SD; *Statistically significant; T-test=Student t-test*

Table 6. Occurrence of adverse effects in the groups

Variables	Group I n=25	Group II n=25	*P*
	Freq (%)	**Freq (%)**	
Vomiting			
Yes	0 (0.0)	0 (0.0)	
No	25 (100.0)	25 (100.0)	-
Bleeding			
Yes	0 (0.0)	0 (0.0)	
No	25 (100.0)	25 (100.0)	-
Fever			
Yes	0 (0.0)	0 (0.0)	-
No	25 (100.0)	25 (100.0)	

4. DISCUSSION

As observed in this study, in children with comparable demographics, suppository diclofenac 2 to 3mg/kg administered rectally in two divided doses, at induction of general anaesthesia and 12 hours thereafter, demonstrated superior analgesic efficacy compared to a single dose of same 2 to 3 mg/kg at induction, characterized by significantly more extended duration of post-operative analgesia; this was evidenced by significantly lower pain scores, a longer time to first analgesic request (TTFAR) and decreased consumption of rescue analgesics, with no significant adverse effects.

Empirical findings over the decades have made evident that non-steroidal anti-inflammatory drugs (NSAIDs), along with their antiplatelet, antipyretic and anti-inflammatory properties, possess postoperative analgesic efficacy, thus decreasing perioperative opioid consumption with its adverse sequelae. Diclofenac sodium, one of the most widely used NSAIDs, is recommended for post adenotonsillectomy analgesia in children [10,11]. Its suitability for use is remarkably enhanced by the fact that it is available in different preparations and, as well, administrable via diverse routes – intravenous, intramuscular, oral, topical and rectal [12,13, 14,15,16].

Low rectal suppository placement, at not more than 1.5 - 2 cm above the external anal sphincter, was adopted in all subjects; this was to confine absorption of diclofenac suppository to the middle and inferior rectal veins, and to circumvent hepatic first-pass metabolism, The rectal route of diclofenac administration entails some remarkable advantages: there is avoidance of the usual pain of intramuscular/intravenous injection, as well as the circumvention of hepatic first-pass metabolism and the consequent decreased bioavailability associated with oral drug administration. Also, according to Jannin et al. [17], the rectal environment is constant, stable, and has reduced enzymatic activity compared to any other part of the gastrointestinal tract. However, there is an inverse correlation between depth of rectal drug insertion and circumvention of hepatic first-pass metabolism. A high rectal drug placement, reaching the anatomical region drained by the superior haemorrhoidal (rectal) veins, will lead to drug absorption into the porto-hepatic circulation and subsequent susceptibility to first-pass metabolism, with deceased drug bioavailability; in contrast, a low rectal insertion, limiting suppository to the region drained by the inferior and middle haemorrhoidal veins, enhances absorption into the inferior vena cava, by-passing the porto-hepatic venous system [18].

Regular pain assessment is key to effective pain management, and pain scores generated from the use of a reliable pain assessment tool are strategic to the achievement of this goal, because a particular pain score is necessary to represent an analgesic request by the patient and, hence, the 'trigger point' for analgesic administration. In this regard, the efficacy of an administered analgesic can be assessed using two important clinical parameters: 1) the extent to which it decreased pain scores below analgesic 'trigger point', and 2) the duration that pain scores remain decreased below the analgesic 'trigger point'. In this study, the administration of suppository diclofenac 2 – 3 mg/kg rectally decreased post adenotonsillectomy pain scores to less than 4, in each of the two groups of children, for the first four hours postoperatively. This finding is similar to those of Adarsh et al. [19].

The administration of 2 – 3 mg/kg rectal diclofenac, in two divided doses, at induction of general anaesthesia and 12 hours thereafter, recorded superior analgesic profile over the group which received a single full dose. Nordbladh et al. [20] investigating the efficacy of diclofenac suppository administered in two divided doses, pre- and postoperatively, on tonsillectomy pain had stated that the group of patients who received rectal 50mg diclofenac, 1 hour before, and at the end of surgery, had a significantly longer TTFAR with lower rescue analgesic consumption, compared to the group which had 100mg inserted only postoperatively. Although, Adarsh et al. [19] used a lower dose of 1 mg/kg diclofenac to achieve similar decreased pain scores, their finding is attributable to the potentiating effect of intramuscular 5 mg/kg ketamine given for preoperative sedation of the children in their study. The sedative and potent analgesic efficacy of ketamine, even in subanaesthetic doses, had been reported [21]. Besides, sedation could be mistaken for analgesia especially in children within the non-verbal age range. In this study ketamine was not administered in any of the groups.

The timing of rectal administration of suppository diclofenac is of strategic relevance to the achievement of optimal analgesic efficacy, considering the mode of action of NSAIDs. Similar to all other NSAIDs, the analgesic actions of diclofenac are effected through the inhibition of pro-inflammatory prostaglandin synthesis through blockade of the enzymatic actions of cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) in the pathway of arachidonic acid metabolism. Currently, extensive scientific research has shown the pharmacological actions of diclofenac to be multimodal and beyond the bounds of COX-1 and COX-2 inhibition [22]. The empirical findings have suggested that diclofenac can affect arachidonic acid release and uptake, cause inhibition of the thromboxane-prostanoid receptor, inhibition of lipoxygenases, substance P and blockade of acid-sensing ion channels, as well as alteration of interleukin-6 production; furthermore, it can also effect inhibition of peroxisome proliferator activated receptor gamma (PPARgamma) and N-methyl-D-aspartate (NMDA).

In this study, rectal administration of diclofenac suppository was done pre-incisionally immediately after induction, with part of the full dose inserted in one group, and the whole dose in the other. Recognizing their modes of action, Campbell et al. [23] opined that the administration of NSAIDs generally should be done before surgical trauma occurs, to prevent nociceptor sensitization. Also, in their study of 80 children aged 2 – 14 years, Swanepoel et al. [15] had demonstrated that preoperative oral diclofenac administered 2 hours prior to tonsillectomy achieved significantly decreased rescue analgesic consumption, compared to same dose of diclofenac administered rectally after induction, thus agreeing with Campbell et al. [23] on the strategic necessity of NSAIDs administration prior to tissue damage. This observation by Swanepoel et al. [15] corroborates the earlier findings by Nordbladh et al. [20].

The analgesic profiles showed comparably decreased median postoperative pain scores, up to the 4th hour between groups I and II in this study; however, from the 6th to 24th hour, the scores were significantly lower in group I, which had rectal 2 – 3 mg/kg suppository diclofenac in two divided doses. As well, the 24-hour total fentanyl and acetaminophen consumptions were significantly lower, with associated significantly longer TTFAR in group I. These observations could be revealing an important fact about rectally administered suppository diclofenac.

Clearly, there are no studies comparing single pre-incisional versus pre-incisional plus 12th hour postoperative suppository diclofenac administration to draw reference from; however, while the reason for the observed superiority in analgesic profile, of the divided dose over the single full dose regimen of rectal diclofenac, in this study, is yet to be fully elucidated, it is most probable that the deposition of relatively larger rectal dose of suppository diclofenac, resulted in a correspondingly greater rate of drug absorption into the systemic circulation, and attracted a commensurately greater enzymatic activity, thus, precipitating faster drug degradation with consequent faster decline in bioavailability, in the event that timely repeat dosing did not occur, as was the case in group II. This same explanation might underpin the similar finding of an association of a comparatively superior analgesic profile with divided dose rectal diclofenac regimen by Nordbladh et al. [20]. Empirically, evidence exists that once in the systemic circulation, diclofenac sodium undergoes rapid metabolism by hepatic enzymes to its hydroxyl metabolites, with resultant decline in plasma bioavailability [24]. Following single intravenous administration in healthy female volunteers, Willis et al. [25] did document that plasma level of diclofenac declined rapidly, reaching levels below detection at 5.5 hours post drug administration. Inferentially, therefore, the pre-incisional rectal administration of suppository diclofenac in divided doses should be considered preferable to single total dose.

The two groups in this study were comparable in their mean TTFOI (in hours) with the values of 4.24±1.85 (Group 1) and 4.72±1.51 (Group 2), p = 0.3212, further depicting the analgesic efficacy of rectally administered suppository diclofenac in post adenotonsillectomy pain management; this observation corroborates the finding that 35 **(**46.67%) of the children given 1 – 1.5 mg/kg suppository diclofenac rectally, in the immediate post adenotonsillectomy period, could swallow their saliva without pain, and commenced oral intake within 0 - 6 hours of full recovery from anaesthesia, as documented by Ibekwe et al. [1].

A feared complication of NSAIDs usage in the perioperative setting is the occurrence of postoperative bleeding. In this study, however, post adenotonsillectomy bleeding was zero (0.0%) similar to the report by Nordbladh et al. [20], and there were no other adverse effects such as fever and vomiting in any of the groups.

5. CONCLUSION

Suppository diclofenac 2 – 3 mg/kg administered rectally, as a single full dose at induction, or in two divided doses given partly at induction and partly at 12 hours postoperatively, demonstrated analgesic efficacy following adenotonsillectomy in children; however, the rectal administration in divided doses was associated with a significantly superior analgesic profile, relative to the single full dose regimen, without the occurrence of any adverse effects.

6. RECOMMENDATION

More studies, especially those incorporating pharmacokinetics, on rectal administration of suppository diclofenac in single versus divided doses are required, to discover additional scientific facts to elucidate reasons for the observed superiority in analgesic profile of the divided dose regimen over the single full dose.

7. LIMITATION

One hundred percent weight-based accuracy in suppository diclofenac administration could not be ensured in this study; the drug used was in solid state, hence prone to loss of some active particles if split. Therefore, a range of 2 – 3 mg/kg was used to avoid drug splitting.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ETHICAL APPROVAL

Ethical approval reference UPTH/ADM/90/S.II/ VOL.XI/1285, granted 25th November, 2021.

CONSENT

As per international standards, parental written consent has been collected and preserved by the author(s).

ACKNOWLEGEMENTS

The authors hereby express gratitude to Matron Charity Omisina and Dr Adonye O. P. Peterside, for their understanding during the period of this research work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ibekwe U, Oghenekaro E. Post-adenotonsillectomy analgesia in children: The place of non-steroidal anti-inflammatory drugs. Port Harcourt Med J. 2019;13:41-45.
   DOI: 10.4103/phmj.phmj_15_18
2. Onotai L, Lilly-Tariah Od. Adenoid and tonsil surgeries in children: How relevant is pre-operative blood grouping and cross-matching? Afr J Paediatr Surg. 2013;10 (3):231-234.
   DOI: 4103/0189-6725.120887
3. Hadden SM, Burke CN, Skotcher S, Voepel-Lewis T. Early postoperative outcomes in children after adenotonsillectomy. J Perianesth Nurs. 2011;26(2):89-95.
4. Loizzo A, Loizzo S, Capasso A. Neurobiology of pain in children: An overview. Open Biochem J. 2009;3:18-25.
   DOI: 10.2174/1874091X00903010018
5. Dunwoody CJ, Krenzischek DA, Pasero C, Rathmell JP, Polomano RC. Assessment, physiological monitoring, and consequences of inadequately treated acute pain. J Perianesth Nurs. 2008;9(1):S15-27.
   DOI: 10.1016/i.iopan.2007.11.007
6. Breivik H. Postoperative pain management: why is it difficult to show that it improves outcome? Eur J Anaesthesiol. 1998;15(6):748-751.
7. Raveendran R, Gitanjali B. A practical approach to PG dissertation. 1st ed. New Delhi, Jaypee Brothers Medical Publisher; 1997:42.
8. Yeganeh-Mogadam A, Fazel MR, Parviz S. Comparison of analgesic effect between gabapentin and diclofenac on postoperative pain in patients undergoing tonsillectomy. Arch Trauma Res. 2012;1(13):108-111
9. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: A behavioural scale for scoring post-operative pain in young children. Pediatr Nurs. 1997;23(3):293-297.
10. Verghese ST, Hannallah RS. Acute pain management in children. Journal of Pain research 2010;3:105-123.
    DOI: 10.2147/jpr.s4554
11. Warltier DC, Marret E, Flahault A, Samama CM, Bonnet F. Effects of postoperative nonsteroidal anti-inflammatory drugs on bleeding risk after tonsillectomy: Meta-analysis of randomized, controlled trials. Anesthesiology 2003;98(6):1497-1502.
    DOI: 0.1097/00000542-200306000-00030
12. Idkaidek NM, Amidon GL, Smith DE, Najib NM, Hassan MM. Determination of the population pharmacokinetic parameters of sustained-release and enteric coated oral formulations, and the suppository formulation of diclofenac sodium by simultaneous data fitting using nonmem. Biopharm Drug Dispos. 1998;19(3):169-174.
    DOI:10.1002/(SICI)1099-081X(199804)19:3<169::AID-BDD83>3.0CO;2-C
13. Tarkkila P, Saarnivaara L. Ketoprofen, diclofenac or ketorolac for pain after tonsillectomy in adults. Br J Anaesth 1999;82:52-60 .
14. Onuorah CM, Fyneface-Ogan S, Aggo AT. The efficacy of diclofenac for post caesarean section analgesia: Comparison of Rectal And Intramuscular Routes. Niger J Med. 2018;272-276.
15. Swanepoel A, Semple P. Oral versus rectal diclofenac for post tonsillectomy pain in children. Anaesthesia 1999;54(3):298-299.
    DOI: 10.1046/j.1365-2044.199.00811.x
16. Talnia S, Fry RR, Sharma A, Patidar DC, Goyal S, Ghandi G. Efficacy of transdermal diclofenac patch as an analgesic following premolar extractions in orthodontic patients. Ann Maxillofac Surg. 2020;10(1):37-41.
    DOI: 10.4103/ams.ams_220_18
17. Jannin V, Lemagnen G, Gueroult P, Larrouture D, Tuleu C. Rectal route in the 21st century to treat children. Adv. Drug Deliv. Rev.2014;73:4-49.
    DOI: 10.1016/j.addr.2014.05.012
18. Hua S. Physiological and pharmacological considerations for rectal drug formulations. Front Pharmacol 2019;16(10):1196.
    DOI: 10.3389/fphar.2019.01196
19. Adarsh ES, Mane R, Sanikop CS, Sagar SM. Effect of preoperative rectal diclofenac suppository on postoperative

analgesic requirement in cleft palate repair: A randomised clinical trial. Indian J Anaesth 2012;56(3):265-269.
DOI: 10.4103/0019-5049.98774
20. Nordbladh B, Ohlander R, Bjorkman R. Analgesia in tonsillectomy: A double-blind study on pre- an post-operative treatment with diclofenac. Clin Otolarngol Allie Sci. 1991;16(6):554-558.
DOI: 10.1111/j.1365-2273.1991.tb00973.x
21. Vadivelu N, Schermer E, Kodumudi V, Belani K, Urman RD, Kaye AD. Role of ketamine for analgesia in adults and children. J Anaesthesiol Clin Pharmacol. 2016;32(3):298-306.
DOI: 10.4103/0970-9185.168149
22. Gan TJ. Diclofenac: An update on its mechanism of action and safety profile. Curr Med Res Opin. 2010;26(7)1715-1731.
DOI: 10.1185/03007995.2010.486301
23. Campbell WI, Kendrick R, Patterson C. Intravenous diclofenac sodium: Does its administration before operation suppress postoperative pain? Anaesthesia 1990;45: 763-766.
24. Willis JV, Kenall MJ, Flinn RM, Thornhill DP, Welling PG. he pharmacokinetics of diclofenac sodium following intravenous and oral administration. Eur J Clin Pharmacol. 1979;16(6):405-410.
DOI: 10.1007/BF00568201

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/120386