Comparison of post-operative pain control and stress response from rectal diclofenac and pre-incisional wound infiltration with bupivacaine in paediatric herniotomy

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Abstract

Background: Herniotomy is one of the most common procedures performed by the paediatric surgeon. Its most common complication is post-operative pain. Furthermore, is the known stress response associated with surgery, which may also have deleterious effects. Analgesics are effective in reducing both these effects. This study compares the effectiveness of two analgesic options- rectal diclofenac and wound-infiltrated bupivacaine, on post-operative pain and stress response.

Methods: This was a prospective, double blinded clinical study. Seventy two children undergoing herniotomy were randomized into group 1 (Bupivacaine group) and group 2 (Diclofenac group). The children were similar in all other aspects except for the treatment they received. Pain was evaluated by a blinded assessor on arrival of the patient in the recovery room using the FLACC scale. Blood samples were taken following induction of anaesthesia and at the end of surgery for cortisol and glucose estimations.

Results: The mean pain scores were similar in both groups post-operatively and it remained below a score of 4 throughout the study period. There was no significant difference between the pre- and post-operative serum cortisol and glucose levels in both groups (p > 0.05)

Conclusion: Rectal diclofenac provides a comparative effectiveness of analgesia to wound-infiltrated bupivacaine in children undergoing herniotomy.

Keywords: *Paediatric herniotomy, Rectal Diclofenac, stress response, pre-incisional wound infiltration, Bupivacaine, post-operative pain.*

Résumé

Contexte: L'herniotomie est l'une des procédures les plus courantes effectuées par les chirurgiens pédiatriques. Sa complication la plus fréquente est

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la douleur post-opératoire. En outre, est la réponse au stress connue associée à la chirurgie, qui peut également avoir des effets délétères. Les analgésiques sont efficaces pour réduire ces deux effets. Cette étude compare l'efficacité de deux options analgésiques - le diclofénac rectal et la bupivacaïne infiltrée par la plaie, sur la douleur post-opératoire et la réponse au stress.

Méthodes: Ceci était une étude clinique prospective, aveuglement doublée. Soixante-douze enfants subissant une herniotomie ont été randomisés dans le groupe 1 (groupe bupivacaïne) et groupe 2 (groupe diclofénac). Les enfants étaient dans tous les autres aspects sauf pour le traitement qu'ils ont reçu. La douleur a été évaluée par un évaluateur aveugle à l'arrivée du patient dans la salle de réveil en utilisant l'échelle FLACC. Des échantillons de sang ont été prélevés après l'induction de l'anesthésie et à la fin de la chirurgie pour les estimations de cortisol et de glucose.

Résultats: Les scores de douleur moyens étaient similaires dans les deux groupes après l'opération et ils sont restés sous le score de 4 tout au long de la période d'étude. Il n'y avait pas de différence significative entre les niveaux de cortisol et de glucose sériques pré- et post-opératoires dans les deux groupes (p> 0,05)

Conclusion: Le diclofénac rectal fournit une efficacité comparative de l'analgésie à la bupivacaïne infiltrée par la plaie chez les enfants subissant une herniotomie.

Mots clés: *Herniotomie pédiatrique, diclofénac rectal, réponse au stress, infiltration pré-incision, bupivacaïne, douleur postopératoire.*

Introduction

Herniotomy is one of the most common procedures performed by paediatric surgeons worldwide [1–3] and it is safely performed as a day-case procedure [4–7]. Post-operative pain has been reported as the commonest complication of this procedure and one of the commonest causes of unanticipated hospital admission after day-case procedures [5,8]. The treatment of pain is, therefore, an integral part of

day-case herniotomy. Various modalities of analgesia exist and multimodal approach to preventing and treating pain is now being employed [9]. The multimodal approach involves combination of mild analgesics with regional and local analgesia to achieve effective pain relief and reduce opioids-related side effects [9–11]. Opioids, which had hitherto been the mainstay in the treatment of acute post-operative pain, are increasingly being avoided because of their documented side effects such as respiratory depression and delayed recovery from anaesthesia [12]. The use of non-opioid analgesics, such as the non-steroidal anti-inflammatory drugs (NSAIDs), is much favoured recently as they are effective and safe in children [12–14]. This practice is, however, not common in developing countries where options of medications may be limited. The use of bupivacaine for wound infiltration and oral paracetamol for post-operative pain are the generally employed methods of post-operative pain management in our centre. Oral paracetamol, however, has been shown to be more effective in children with mild to moderate pain [15].

Surgery is associated with stress response, which is increased in the presence of post-operative pain, due to secretion of cortisol and other stress response hormones [16–18]. This response can be attenuated by various analgesic modalities. Stress response hormone levels can, therefore, be used as an objective method of assessment of the analgesic efficacy of these modalities [16,19].

The aim of this study was to compare the effect of rectal diclofenac and wound-infiltrated bupivacaine on post-operative pain and cortisol levels in children undergoing herniotomy in our centre.

Materials and methods

This was a prospective, randomized, double-blinded clinical study of 72 children that underwent unilateral herniotomy at the University College Hospital (UCH), Ibadan, Nigeria between July 2013 and October 2014. Ethical approval was obtained from the Joint University of Ibadan and University College Hospital Ethics Review Committee and the Oyo State Research Ethical Review Committee. ASA class I or II patients (of consenting parents) with congenital inguinal hernias and hydroceles undergoing herniotomy in the Paediatric Surgery Unit, UCH were recruited for the study. While patients with bilateral, recurrent and complicated hernias, undescended testes, history of dyspepsia and known allergies to either test agents used were excluded from this study.

No premedication was given. General anaesthesia was induced and maintained using isoflurane and oxygen via facemask in younger children and laryngeal mask in older children, with spontaneous respiration. All patients were given a single dose of intravenous fentanyl (at a dose of 1 µg Kg⁻¹) as intra-operative analgesia (protocol followed in our centre) immediately after the induction of anaesthesia. Routine intra-operative monitoring was used.

Patients were randomly assigned to two groups. Patients in the Bupivacaine group (Group 1) had the operation site infiltrated with bupivacaine, 0.5 ml Kg⁻¹ at a concentration of 2.5 mg ml⁻¹, immediately after induction of anaesthesia and two minutes before making the incision. Those in the diclofenac group (Group 2) had rectal diclofenac administered at a dose of 1-2 mg Kg⁻¹ immediately after the induction of anaesthesia, and two minutes before incision was made, while no skin infiltration was done. Diclofenac suppository preparations of 12.5 mg were used and whole preparations were administered at all times, ensuring that the given dose fell within the recommended dose range. We avoided breaking the suppositories to avoid the uncertainty about the drug distribution within the suppository. Standard surgical procedure of herniotomy was performed on all the patients. The same surgical team performed all the surgeries. The patients' peri-operative pulse rate, respiratory rate and blood pressure were recorded. The length of incision, duration of procedure and estimated blood loss in each case were determined and recorded.

Pain measurement

In the recovery room, pain assessments were done at 15 minutes, one hour, two hours and four hours by independent anaesthetists, who were not involved in the procedures and were blinded to the group that the patients were allocated to. The University of Michigan Health System "FLACC" scale [20] was used for an objective assessment of pain (Table 1). Patients with pain score > 4 were treated with intravenous paracetamol or pentazocine as rescue analgesics. The time and frequency of giving rescue analgesia were also recorded.

Endocrine measurement

Venous blood samples were obtained from each patient for the estimation of cortisol and glucose 1-2 minutes after induction of anaesthesia and before administration of the test drug, and 1-2 minutes after the last stitch (before recovery from anaesthesia). Enzyme linked immunosorbent assay (ELISA) was

used to measure the serum cortisol levels (GenWay Biotech Inc. ELISA Cortisol Kit, San Diego, US). Serum glucose estimation was done using the Contour® Glucometer (Bayer Health Care LLC, Mishawaka, IN 46544, USA), in which a drop of blood was placed on a strip, which was then inserted into the reader to give an automatic estimation of the glucose level.

Statistical analysis

Data obtained were analysed using SPSS version 21 software. The sample size was determined with the formula for comparing means using the mean and standard deviations from a previous study and using a power of 80% [21,22]. Values were expressed as mean ± standard deviation. Logarithmic transformation of the serum cortisol levels was done and comparison of means between the study groups was achieved using the Independent t-test. Paired sample t test was used to analyse the differences between pre- and post-operative serum cortisol and

glucose levels in all the participants. Categorical variables were analyzed using the Chi Square and the Fisher's Exact Test. A p value of < 0.05 was considered significant.

Results

A total of 72 patients (36 in each group) were recruited for this study. Their ages ranged from six months to 12 years, with a mean of 61.86 ± 43.86 months. There was no significant difference between the two groups with regards to the ages of patients, their weights and length of surgical incisions (Table 2). The two groups were also similar in terms of the length of pre-operative fast and duration of surgery. There was no significant difference between the mean FLACC pain score in both groups at the various times of assessment (Table 3). The mean pain score in both groups remained below 4 for the entire four hours of assessment. The mean pain score reduced from a maximum at the time of first assessment to a minimum by the fourth hour of assessment (Fig. 1).

Table 1. FLACC Pain Score

	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth. tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaints	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching. hugging or "talking to : distracable	Difficult to console or comfort

Table 2. Patients' characteristics, clinical data, duration of surgery, length of pre-operative fast, length of incision and rescue analgesia requirement.

	Bupivacaine group (Group 1, $n = 36$)	Diclofenac group (Group 2, $n = 36$)	95% confidence interval of the difference
Age (months)	66.61 ± 46.77	57.11 ± 40.85	-11.14 – 30.14
Sex (M/F)	31/5	34/2	
Weight (Kg)	20.56 ± 11.61	17.56 ± 8.22	-1.74 – 7.72
Heart rate			
Pre-operative	102.61 ± 21.27	104.67 ± 27.92	-13.72 – 9.61
Post-operative	111.00 ± 20.12	110.03 ± 23.76	-9.38 – 11.32
Duration of surgery (mins)	35.91 ± 12.78	36.77 ± 11.35	-6.62 – 4.91
Length of pre-operative			
fast (hours)	15.13 ± 9.53	13.48 ± 3.20	-1.70 – 4.99
Length of incision (cm)	3.27 ± 0.59	3.30 ± 0.69	-0.82 – 0.10
Rescue analgesia	4	3	

Values are expressed in mean ± SD

Table 3. FLACC pain scores

	Bupivacaine group	Diclofenac group	95% confidence interval of the difference
FLACC at 15 mins	1.36 ± 2.80	0.89 ± 2.14	-0.70 – 1.64
FLACC at 1 hour	1.19 ± 2.42	0.50 ± 1.52	-0.26 – 1.65
FLACC at 2 hours	0.56 ± 1.23	0.28 ± 0.78	-0.21 – 0.76
FLACC at 4 hours	0.17 ± 0.45	0.14 ± 0.83	-0.29 – 0.34

Values are expressed in mean ± SD

Four patients in Group 1 had rescue analgesia (intravenous paracetamol) for FLACC pain score of > 4, while 3 in Group 2 required rescue analgesia. These patients had the rescue analgesics after the first assessment, except for 2 (1 in each group), who required it after the second assessment. None of them

There was no significant difference between the baseline serum cortisol levels of both groups (Table 4). The post-operative serum cortisol level was significantly higher than at baseline in the bupivacaine group but not in the rectal diclofenac group (p = 0.008 in Group 1 and p = 0.127 in Group
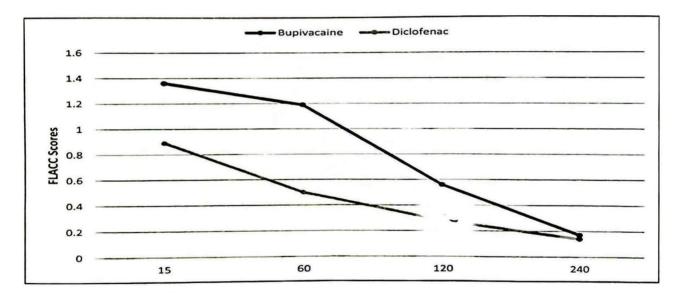

Table 4. Cortisol and Glucose values

	Bupivacaine group	Diclofenac group	95% confidence interval of the difference
Serum Cortisol (ng ml^{-1})			
Pre-operative	234.77 ± 191.69	284.92 ± 279.83	-179.45 – 79.17
Post-operative	430.30 ± 355.37	396.21 ± 316.16	-148.07 – 216.25
Serum Glucose (mg dl^{-1})			
Pre-operative	74.49 ± 10.28	81.27 ± 31.60	-17.95 – 4.40
Post-operative	102.14 ± 41.48	129.66 ± 93.09	-61.67 – 6.63

Values are expressed in mean ± SD

required a repeat dose of rescue analgesia. There was no significant difference between the two groups in terms of the patients' requirement for rescue analgesia.

2). There was, however, no significant difference between the mean post-operative serum cortisol levels in the two groups. The serum glucose levels also followed a similar trend to that of serum cortisol.

The pre-operative heart rates were also similar in both groups with a consistent and also similar increase post-operatively. There was no significant difference in the estimated blood loss between the two groups.

Discussion

Hernia repair in children is a day-case surgery. Hence, most of the post-operative care is carried out at home and by the parents. Pain is the most common complication and cause of unanticipated hospital admission following day-case procedures with much of this being underplayed and pain relief often inadequate [5,8,23].

Multimodal approach, which involves the combination of two or more modalities to prevent and treat pain, has been advocated [24]. Pre-incisional and post-incisional infiltration of the wound with levobupivacaine, caudal anaesthesia and the use of intra-muscular and suppository diclofenac have all been shown to be effective modalities. They reduce the requirement for opioids, increase the duration of post-operative analgesia and promote early recovery [8,16,25,26]. Bupivacaine, a long-acting anaesthetic agent, has been variously shown to be effective for post-operative pain but is also known to be associated with systemic toxicity when inadvertently administered into the vascular system [24,27,28]. This has stimulated interest in the administration of alternative agents.

The use of NSAIDs is not popular in our centre and most other centres across Nigeria. The protocol for the treatment of post-operative pain has been limited to the use of wound-infiltration with either lidocaine or bupivacaine at the end of surgery, in addition to oral paracetamol, which is given as the take-home medication.

This study provides evidence that either infiltrating the wound with bupivacaine or administering rectal diclofenac pre-operatively was effective for post-operative analgesia following herniotomy in children. In the present study, the mean pain scores remained low (< 4) throughout the post-operative study period in both groups. The mean pain score (FLACC scale) in both study groups gradually fell from a maximum in the immediate post-operative period to a minimum at 4 hours. Solanki *et al* in a comparison of bupivacaine infiltration and diclofenac suppository in 50 patients undergoing tonsillectomy found the latter to be a better option in terms of its convenience and duration of analgesia [29]. However, the pain experience of the patient and the effectiveness of analgesia of the test drugs may be different between tonsillectomy and herniotomy.

The mean pain score was relatively higher in the immediate post-operative period in both groups in the present study. This is similar to what was reported by Moores *et al*, who studied post-operative analgesia in 43 children, comparing rectal diclofenac to caudal bupivacaine [30]. They reported that rectal diclofenac was less potent in the immediate post-operative period but of comparable efficacy to caudal blockade after two hours. This delayed efficacy was ascribed to the possibility of some delay in the absorption of diclofenac from the rectal mucosa [30]. This report did not agree with our study in which, bupivacaine infiltration was not more effective but comparable to rectal diclofenac as the mean pain score at 15 minutes and 1 hour post-operation were comparable to the rectal diclofenac group.

The present study showed a comparable analgesic efficacy between rectal diclofenac and bupivacaine wound infiltration. Gupta *et al*, in a similar comparative study of the analgesic efficacy of rectal diclofenac and caudal block alone reported a mean duration of analgesia of 12.45 hours with rectal diclofenac administered at a dose of 1 mg Kg $^{-1}$ as against 8.2 hours provided with caudal block [25]. Gupta *et al* in that study noted that rectal diclofenac alone or in combination with caudal block provided excellent analgesia and lasted for a longer time than caudal block alone in children undergoing infra-umbilical surgeries [25]. Gupta *et al*, however, also observed the delay in the onset of analgesia with diclofenac when compared to caudal block as reported by Moores *et al*. The mean pain scores only became comparable at 1 hour post-operation [25]. This delay was not observed in our study, similar to the findings of the study by Solanki *et al* [29]. This difference in the onset of analgesia was ascribed to the dose of rectal diclofenac used in the study by Solanki *et al*, which was 2mg Kg^{-1} as against 1mg Kg^{-1} used in the studies by Moores *et al* and Gupta *et al*. A dose of 1 to 2mg Kg^{-1} of rectal diclofenac was used in this study to avoid having to divide the suppositories. The 12.5mg formulation of rectal diclofenac was used for this study. Whole suppositories were, therefore, used ensuring that the dose given fell within the specified range. It is possible that difference in dosage in the various studies is responsible for the variation in the findings on the onset of analgesic efficacy of rectal diclofenac.

Three of the patients in the diclofenac group and four in the bupivacaine group required additional analgesics for pain scores greater than 4. This is comparable to the study by Moores *et al* who reported comparable requirement for additional analgesia between patients who had rectal diclofenac

and those who had caudal bupivacaine for day-case herniotomy [30].

The serum cortisol level is expected to rise as part of the usual stress response to surgery. The level of rise can, however, be reduced by attenuation of the stress response, which can be achieved by various analgesic modalities [16]. The mean baseline serum cortisol level in this study (259.39 ng ml^{-1}) falls within the range of 60 to 300ng ml^{-1} estimated for adult Nigerians at the University College Hospital, Ibadan [31] and the levels were comparable in both groups. There was comparable difference between pre- and post-op serum cortisol levels between both groups. This finding corroborates our finding of a comparable mean pain scores between the two study groups. There was a similar trend in the serum glucose response in this study, which mirrored that of the serum cortisol response.

Theoretically, NSAIDs can cause increased bleeding because of their known anti-platelets effect. None of the participants in this study, however, was observed to have excessive bleeding following surgery and estimated blood loss was comparable between the two groups. A similar finding was reported by Adarsh *et al* who found no significant bleeding in excess of usual in children who had pre-operative rectal diclofenac for cleft palate repair [12]. No incident of significant post-operative bleeding was also reported in the studies by Gupta *et al* and Moores *et al* [25,30]. This finding also agrees with the conclusion by the Cochrane review on the safety of the use of diclofenac in children and the review by Rømsing and Walther-Larsen [13,14]. These reviews on the use of NSAIDs noted no excessive bleeding in any child and found no difference in the rates of bleeding requiring surgical intervention in tonsillectomy (a high risk surgery for bleeding) between participants randomized to diclofenac and non-NSAIDs. We, however, excluded patients with either personal or family history of asthma or dyspepsia because of the known effects of NSAIDs on prostaglandin synthesis. No adverse drug reaction was recorded amongst any of the participants in this study. A major limitation of this study was the subjective nature of the FLACC scale that was used for the evaluation of pain control. In a way to reduce this subjectivity bias, we compared the vital signs, which were noted to change with experience of pain in children.

Conclusion

Rectal diclofenac provides a comparative effectiveness of analgesia to wound-infiltrated bupivacaine in children aged six months and older undergoing day-case herniotomies. It also has similar effects on stress response to surgery, measured with serum cortisol and blood glucose, in the early post-operative period to that produced by bupivacaine infiltration. It can be safely given to patients who do not have personal or family history of asthma, dyspepsia, bleeding diathesis and known allergy to NSAIDs. The findings of the current study suggest that rectal diclofenac is an effective alternative to bupivacaine infiltration for early post-operative analgesia in children.

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