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RESEARCH ARTICLE

Comparison of a Combination of Caudal Levobupivacaine with Fentanyl and Levobupivacaine Alone for Alleviating Postoperative Pain During Infraumbilical Procedures in Children Under 3 Years

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Abstract:

Background:

To compare the post-operative analgesic efficacy of caudal blockade using levobupivacaine alone and a combination of fentanyl with levobupivacaine in children under 3 years undergoing infraumbilical surgeries. Combination of levobupivacaine with fentanyl and levobupivacaine alone in children for caudal block was never studied before. Hence there was a need for the study.

Methods:

After approval from Institutional Ethical Committee, Kasturba Medical College, Mangaluru, 60 patients of age group 0-3 years, either sex of ASA physical status 1 and 2 undergoing infraumbilical surgeries were chosen after written parental consent and were randomised into 2 groups of 30 each L and LF using computer generated block randomisation to receive caudal blocks. Post operatively assessed for pain using CHIPPS scale at 2, 4, 6, 12 and 24 hours and compared in both groups.

Results:

Out of 60 patients, 30 in each group [L and LF], CHIPPS scores at 2, 4, 6, 12 and 24 hours post-operatively exhibited a p-value of 0.545, 0.492, 0.626, 0.166, and 0.329 respectively [not significant]. Mean duration of analgesia was 14.60 in Group L & 17.67 in Group LF with a t test p value of 0.119 [not significant].

Conclusion:

Combination of fentanyl with levobupivacaine when compared to levobupivacaine alone for caudal block was equianalgesic in children less than 3 years undergoing infra umbilical procedures.

Keywords: Caudal block, Fentanyl, Levobupivacaine, Post-operative pain, Infraumbilical, CHIPPS.

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1. INTRODUCTION

Pediatric pain management during surgery and in postoperative period has made tremendous progress over the years in spite of inadequate research, fear of opioid-induced respiratory depression and possible addiction. Advances in the understanding of pediatric neurobiology with the availability of novel analgesics, a multimodal approach of using systemic opioids, non-steroidal anti-inflammatory drugs and regional techniques with or without adjuvants were practiced alone or in combinations. Caudal block is one of the main modes of postoperative analgesia in children for infra umbilical surgeries [1]. Local anaesthetics which are commonly used in the caudal block are bupivacaine, levobupivacaine, and ropivacaine in different concentrations with additives like fentanyl, morphine, butorphanol, tramadol, clonidine, dexmedetomidine and dexamethasone which are added to improve their efficacy [2, 3]. Epinephrine 1:200000 concentrations mixed with local anaesthetics marginally prolonged the effect of hydrophilic lignocaine but failed to do so with lipophilic bupivacaine due to its fat absorption and slow release [4]. Levobupivacaine is the S [–] enantiomer of racemic bupivacaine and the evidence suggests that it retains similar properties but less cardio toxic which is often fatal as observed with racemic bupivacaine [5 - 7]. Considering the useful properties of the above drug, a study

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was conducted aiming at a comparison of a combination of caudal 0.25% levobupivacaine with fentanyl 1µg/kg and levobupivacaine alone for alleviating postoperative pain during infra umbilical procedures in children under 3 years. Fentanyl is a synthetic opioid agonist, readily crosses the lumbar dura matter, penetrates rapidly the lipid moiety of underlying cord tissue and helps in the prevention of rostral migration of fentanyl avoiding central nervous system dependent depression of respiratory and cardiovascular system [3]. The most difficult task of pain management in children is the accuracy of assessment and obtaining a proper objective compelled us to adopt a simple Children and Infant Postoperative Pain Scale (CHIPPS) to assess pain in immediate post-operative period. Hence, we took up this study to compare analgesic efficacy of the two drugs and more so challenging the paediatric population.

2. MATERIALS AND METHODS

A double-blinded, prospective, randomized, clinical trial was conducted in a state-owned pediatric tertiary care teaching hospital, from October 2016 to June 2018 after obtaining approval from Institutional Ethics Committee dated on 18th January 2018. Sixty ASA 1 and 2 children aged less than 3 years weighing less than 15 Kg posted for infra umbilical surgeries were chosen. The study procedure was explained to the parents, who took written informed consent. Children of ASA status 3 and 4, with a history of allergy to any of the drugs used in the study, hemodynamically unstable patient, acute emergencies, surgery duration more than 90 min, and who refused to give consent were excluded.

Premedication was done with midazolam 0.02mg/kg in the pre-op holding area. On receiving the patients in the operating room, standard ASA monitors were connected. Patients of both the groups were induced with titrated doses of propofol followed by atracurium [0.5mg/kg] to facilitate intubation with appropriate sized endotracheal tubes, and were maintained on N_2O and O_2 50% each with 2% sevoflurane. All 60 patients were randomized into group L and group LF of 30 each *via* computer generated block randomization. Patients belonging to Group L received 0.25% levobupivacaine 2mg/kg and Group LF received a combination of fentanyl 1µg/kg and 0.25% levobupivacaine2 mg/kg *via* the caudal route. After inducing these patients, they were put in the left lateral position and under aseptic conditions, a caudal block was performed using a 22 G needle with 0.25% levobupivacaine diluted in normal saline in the L group and the other group LF received the same with fentanyl 1 µg/kg. Immediately after the caudal block, the patients were returned to the supine position for performing the surgical procedure. Skin incision was allowed strictly after 15 min of block procedure and hemodynamic variables were monitored in all patients after surgical incision followed by every 10 min till the end of the surgery. No intravenous supplementation of opioids or per-rectal analgesic suppository drugs was given to any patient perioperatively. Any patient responding to the incision with an increase in blood pressure [>10 mmHg] or heart rate [>10 beats/min], was considered as the failure of the caudal block. These patients were excluded from the study and rescue analgesia was given. Intravenous tramadol 1mg/kg or 20mg/kg paracetamol suppository was used. Those surgeries which went beyond 90 min were excluded. Postoperative pain assessment was carried out by anaesthesiologists who were unaware of the present study using Children's and Infant's Postoperative Pain Scale [CHIPPS] which includes 5 characteristics [8]. The final score was calculated by collecting every 5 individual scores [ranging from the minimum score of 0 to the maximum 10]. Postoperative analgesia was supplemented to those children whose scores were more than 4 with paracetamol suppository 20mg/kg or intravenous tramadol 1mg/kg. Following clinical parameters were recorded:

[1] Intraoperative heart rate and blood pressure monitoring done every 10 minutes including pre and post induction.

[2] Post-operatively pain scale was monitored at 2,4,6,12 and 24 hours by using CHIPPS scale.

[3] Postoperatively monitored for blood pressure, heart rate at 2, 4,6,12 and 24 hours.

[4] Side effects.

3. STATISTICAL ANALYSIS

Data measurements were done using

$n = 2[Z_\alpha + Z_\beta]^2 x\ \sigma^2 / d^2$

Where: $Z\alpha = 1.96$ at 95% confidence interval

$Z\beta = 1.28$ at 90% power

σ = SD

d = mean difference

With 95% confidence interval & 90% power with respect to $\sigma = 0.3$ & $d = 0.11$ the sample size was designated 30 in each group [n=30×2=60] $d = 0.11$. Data analysis was done using fisher's exact p test; chi square test, student paired t test. A statistical package SPSS version 17.0 was used and a p value <0.05 was considered significant.

4. RESULTS

As per Table **1**, 16.7% of the patients belonged to the age group less than 1year in group L and 10% of patients belonged to the age group less than 1 year in group LF. 50% belonged to the age group between 1 to 2 years in both the groups L and LF. Ten patients above 2yrs belonged to L group and 12 belonged to group LF 33% and 36.7%, respectively. The age parameters were not significant considering both the groups (p value>0.05) and the mean weight of the 30 patients belonging to group L was 12.02 kg with a standard deviation of 2.712. In the group LF, the mean weight was 12.48 with a standard deviation of 2.269 with the p value remaining not significant (0.495).

As per Fig. (**1**), 5 patients in group L were female (16.7%) and 6 in group LF were females whereas 25 patients in group L (33.3%) and 24 in group LF (30%) were males with no significance compared to both the groups (p value > 0.05).

The overall demographic profile compared between the two groups L and LF was not statistically significant with a p value > 0.05.

Table 1. Age and weight comparison of two groups.

Factor	Group	N	Mean	SD	t Test
Weight	L	30	12.02	2.712	0.495
	LF	30	12.48	2.269	NS
Age	L	30	2.727	2.133	0.745
	LF	30	2.91	2.213	NS

Values presented are presented in terms of Mean±SD. Where $p < 0.05$ is considered as significant. L = Levobupivacaine,LF= Levobupivacaine with fentanyl, N= number of patients in the group, SD = standard deviation, NS= not significant.

The heart rate, mean arterial blood pressure in the pre induction, post induction period and thereafter every 10 minutes up to 90 minutes in both groups were statistically insignificant. Average p value > 0.05.

CHIPPS scale in the first two hours remained at 1 and at 2 in the subsequent four hours in the L group. In the subsequent 6, 12 and 24hours, the average CHIPPS score remained at 5, 7 and 8 respectively in the L group. 4 patients in group L exhibited a score of >4 in the first 6hours, 16 patients scored >4 at the end of 12 and 24 hours respectively in the same group. None of the patients scored <4 beyond 24hours in L group. The patients depicting scores above 4 received rescue analgesia with tramadol 1mg/kg body weight or 20 mg/kg paracetamol suppository. As per Table **2** and Fig. (**2**), the difference in CHIPPS score at 2, 4,6, 12 and 24 hours between Group L and Group LF was statistically not significant. As per Table **3**, the mean duration of analgesia in group L was 14.6 hours with a standard deviation of 7.793 and 17.67 in group LF with a standard deviation of 7.222 with no significance compared between both the groups (p value 0.119).

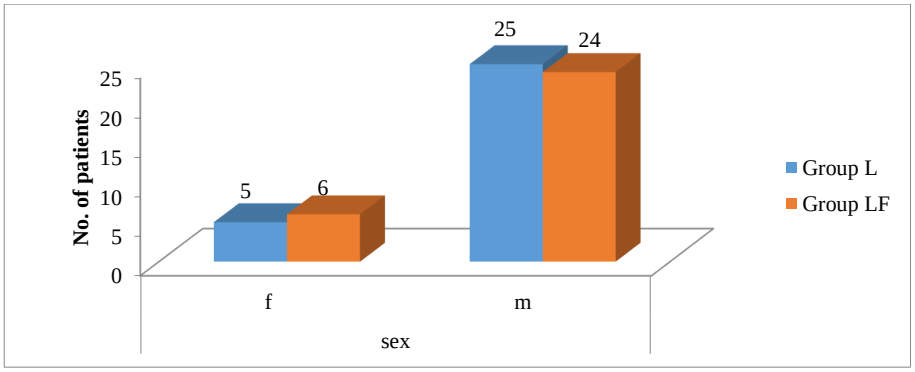

Fig (1). Depicting the bar diagram of sex wise distribution among the two groups. Which is statistically not significant. where L = levobupivacaine, LF = levobupivacaine with fentanyl, f = female, m= male.

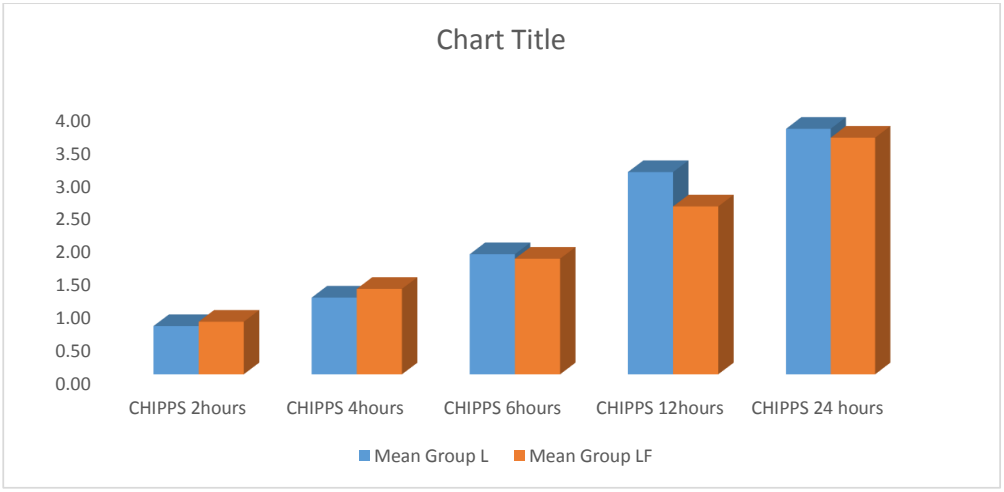

Fig. (2). Bar diagram depicting the mean of CHIPPS scale at 2, 4, 6, 12, 24 hours.
Bar diagram depicting mean of CHIPPS scale at 2, 4, 6, 12, 24 hours. CHIPPS scale = Children's and Infant's Postoperative Pain Scale, L = Levobupivacaine, LF= Levobupivacaine with fentanyl.

Table 2. Comparison of CHIPPS scale between two groups.

	Group	N	Mean	SD	Median	Man Whitney Test Z value	p value	Fisher's Exact p Test
CHIPPS 2hours	L	30	0.73	0.828	1.00	0.03	0.974	0.545
	LF	30	0.80	0.997	1.00		NS	NS
CHIPPS 4hours	L	30	1.17	1.289	1.00	0.92	0.357	0.492
	LF	30	1.30	1.088	1.00		NS	NS
CHIPPS 6hours	L	29	1.83	1.365	2.00	0.11	0.916	0.626
	LF	29	1.76	1.057	2.00		NS	NS
CHIPPS 12hours	L	28	3.07	1.942	4.00	1.18	0.236	0.166
	LF	29	2.55	1.502	3.00		NS	NS
CHIPPS 24 hours	L	22	3.73	2.164	4.50	0.66	0.509	0.329
	LF	27	3.59	1.693	4.00		NS	NS

Values represented in terms of Mean± SD, Median, Mann Whitney test Z value, fisher's exact p test.CHIPPS scale at 2,4,6,12,24 hours was postoperatively. Where $p < 0.05$ is considered as significant. CHIPPS scale = Children's and Infant's Postoperative Pain Scale,L = Levobupivacaine, LF= Levobupivacaine with fentanyl, N= number of patients in the group, SD = standard deviation, NS= not significant.

Table 3. Comparing the duration of analgesia in both groups.

Group	N	Mean	SD	p value
Group L	30	14.60	7.793	0.119
Group LF	30	17.67	7.222	NS

Comparing the duration of analgesia in both groups. Values represented in terms of Mean ± SD. Where $p < 0.05$ is considered as significant.L = Levobupivacaine, LF= Levobupivacaine with fentanyl, N= number of patients in the group, SD = standard deviation, NS= not significant.

Table 4. Children and infants postoperative pain scale [CHIPPS] [8].

ITEM	STRUCTURE	POINTS
Crying	None	0
	Moaning	1
	Screaming	2
Facial expression	Relaxed/Smiling	0
	Wry mouth	1
	Grimace	2
Posture of trunk	Neutral	0
	Variable	1
	Rear up	2
Posture of legs	Neutral, released	0
	Kicking about	1
	Tightened legs	2
Motor restlessness	None	0
	Moderate	1
	Restless	2

5. DISCUSSION

Pain management in the pediatric age group is quite challenging and difficult. Among regional techniques, caudal block and to a lesser extent lumbar epidural are the most commonly used. Regional anaesthesia is a preferred and approved technique wherever feasible in children supplementing good analgesia with minimal physiologic alterations and reducing the usage of potent inhalational anaesthetic agents and opioids helping in faster recovery. Complications with caudal blocks in children are very rare and should be considered for any child undergoing surgery requiring immediate post-operative analgesia for a significant time [9, 10]. Several neurological and cardiovascular adverse reactions with fatalities were reported after inadvertent intravascular injection or during intravenous regional anaesthesia were attributed to the R [+] isomer of bupivacaine [11]. The levorotatory isomers when added were revealed to have a harmless pharmacological profile as their local anaesthetic effects were claimed mainly through the reversible blockage of sodium channels of nerve conduction [12, 13]. It is mainly

combined with general anaesthesia in children for perioperative and post-operative analgesia, labor analgesia and as well as management of acute and chronic pain [12]. The rarely seen adverse effects associated with levobupivacaine are hypotension, nausea, vomiting, headache, site pain, allergic reaction to drug and dizziness [12, 13]. Ivani *et al*. examined three separate concentrations of caudal levobupivacaine [0.125%, 0.20%, and 0.25%] in a study in children between1 to 7 years of age undergoing infra umbilical surgery studied a dose-response liaison equally with an average interval of postoperative analgesia and the number of patients who disclosed evidence of early postoperative motor block [14]. He established that patients who received 0.125% levobupivacaine were free of postoperative residual motor block, whereas the number of patients with residual motor block amplified with 0.20% and 0.25% levobupivacaine. Although levobupivacaine 0.125% seemed to have clinical benefits in this patient group, but also carried the disadvantage of a limited duration of postoperativeanalgesia. B. Locatelli *et al.* [15] conducted a study comparing the analgesic efficacy of an equal concentration of 0.25% of levobupivacaine, ropivacaine and bupivacaine through caudal route for sub umbilical surgeries. They found bupivacaine produced a higher incidence of residual motor block and longer analgesic effect than ropivacaine and levobupivacaine. Most of the infra umbilical surgeries in children below 3 years are the herniotomies, orchidopexies, genitourinary and lower limb orthopedic surgeries lasting below 90 minutes which are usually managed by single shot caudal anesthesia [16]. Considering these problems, Constant *et al.* [17] in 1998, proposed that the addition of clonidine or fentanyl to local anaesthetics prolonged the duration of surgical analgesia after single shot caudal block in children in first four hours post operatively with vomiting being the sole complication. Desai *et al.* [18] in 2008 compared two doses [0.5μg/kg and 1 μg/kg] of fentanyl with bupivacaine through caudal anesthesia and analgesia. They concluded that both the doses of fentanyl provided satisfactory surgical anaesthesia without any hemodynamic disturbances; however, the duration of analgesia with 1μg/ kg of fentanyl was longer. Lerman *et al.* [11] in 2003 in their multicenter trial on efficiency, security, and pharmacokinetics of levobupivacaine with or without fentanyl after continuous epidural infusion, observed 0.0625% levobupivacaine deprived of fentanyl was an effective perioperative epidural solution in children when infused at a rate of 0.3 mg/kg/h. Doctor *et al.* [19] analysed the addition of fentanyl [1μg/ml] to 0.25% bupivacaine and 0.2% ropivacaine for the caudal block during infra umbilical surgeries in children had no difference in the duration of analgesia but less motor blockade was observed in patients with ropivacaine.

A similar study conducted by Atilla *et al.* [20] in 2008, where they compared caudal levobupivacaine with and without sufentanil for postoperative pain management in children concluded that there was no significant difference between the groups.

In the current study, there were no statistically significant changes in hemodynamics in terms of pulse rate and blood pressure at all intervals. The mean duration of action in group L who received levobupivacaine alone was 14.6h whereas it was 17.6h in group LF. The duration of action compared with both the groups was not statistically significant in spite of adding fentanyl due to its lipophilic property and the dose of 1μg/kg was inadequate. Moreover, our surgeries lasted not more than 90 min without warranting the need for epidural catheters for a combined continuous infusion of both the opioids and local anaesthetics. The CHIPPS score remained below 4 in both the groups in the first 6hrs and thereafter remained above 4 at 12 to 24 hours who required rescue analgesia but statistically not significant between the 2 groups. The pain scores remained below 4 in a few patients at 24 hours in both the groups but statistically insignificant.

Another significant finding in this study was we fixed our dose of levobupivacaine at 2 mg/kg in both the groups L and LF and 1μg/kg of fentanyl in group LF diluted to achieve a block up to T10. The levels might have been difficult to assess in anaesthetized children as we believed in the responses of heart rate and blood pressures to incision which would have been better supported with fluoroscopic confirmation of levels using radiopaque dye for dilution.

Although the concentration of levobupivacaine and fentanyl altered with dilution with normal saline, we believed in the concept "High volume low concentration regimen produces more prolonged analgesia and less motor block than Low volume high concentration solution". This concept was strongly supported by Ivani *et al.* [14]. Assessment of residual motor blockade was not performed in the current study with levobupivacaine but Ivani *et al.* [21] in the same study opined that levobupivacaine is known to produce early resolution than bupivacaine or ropivacaine due to its differential blockade property.

Wong *et al.* [22] in 2009 also supported the usage of lower concentration and higher volume of local anaesthetic ropivacaine using 2 different concentration with a fixed dose of 2.25mg/kg. They noticed a better median spread level using radio opaque dye the overall postoperative pain and recovery scores significantly did not alter with low volume high concentration group. A study done by Attri *et al.* [23] concluded levobupivacaine with fentanyl produced rapid onset and duration of sensory and motor block and postoperative analgesia in spinal anaesthesia in adult patients undergoing infra umbilical surgeries.In our study the route was caudal with general anaesthesia, paediatric population and we had not aimed at motor blockade. Our study wanted to assess postoperative analgesia comparatively with the two drugs in children which finally proved both have equianalgesic effect and caudal route is the most preferred route for analgesia in children.

Although ample studies are not available in literature the main pitfalls in this project could have been improved by increasing the sample size and dose of fentanyl for better results. It is still uncertain whether the volume or concentration of local anaesthetic effects its spread and superiority of caudal analgesia when the aggregate drug dose is fixed. Low concentration and large volume of the local anaesthetic agents used may result in differential block in children because of the A-delta and C fibers, and the shorter distances between the nodes of Ranvier [18].

Another limitation of this study was our post-operative follow-up ceased at 24 hours and we are not sure that simple administration of opioids as intermittent boluses or infusion would have given similar or better results.

CONCLUSION

In the current study, the addition of fentanyl as an adjuvant to a single shot caudal anaesthesia did not offer any benefits over plain levobupivacaine in terms of duration of pain relief. It can be still considered as a useful technique without any side effects in minor infra umbilical surgeries like herniotomies and orchidopexies where there is no need for continuous analgesia through epidural catheters and subsequent infusion.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was obatined by Institutional Ethics Committee, India.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

The study procedure was explained to the parents, who took written informed consent.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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