Original Article

Efficacy of caudal fentanyl and ketamine on post-operative pain and neuroendocrine stress response in children undergoing infraumbilical and perineal surgery: A pilot study

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Abstract

Background and Aims: It is well-known that neuroendocrine stress response (NESR) occurs in children and it can be modified by caudal block. However, there is paucity of literature comparing caudal fentanyl and ketamine on NESR. The present study was aimed to compare the analgesic efficacy of these caudal adjuvants and their effect on (NESR) in children undergoing infraumbilical and perineal surgery.

Materials and Methods: A total of 60 children undergoing infraumbilical surgery were included in this randomized, double-blind study. Three groups of 20 each were assigned to receive caudal block with bupivacaine 0.25% 1 ml/kg along with either 0.9% normal saline (Group I) 1 μg/kg fentanyl (Group II) or 0.5 mg/kg ketamine (Group III). Modified visual analogue scale (VAS) was used for assessment of post-operative pain, and stress response was assessed by blood glucose, serum cortisol and insulin levels at various time intervals

Results: VAS scores were significantly lower in the ketamine group at all-time intervals upto 4 h ($P < 0.05$). Patients in ketamine group required rescue analgesia significantly later (8.23 h) when compared to fentanyl (5.95 h) and bupivacaine group (4.10 h). Caudal block led to significant decrease in cortisol and insulin levels within the groups however this significance was not achieved between groups.

Conclusion: Caudal ketamine in a dose of 0.5 mg/kg provides prolonged analgesia when compared to fentanyl 1 μg/kg. Blunting of the NESR was observed in all the groups though the indicators of the response were lowest with ketamine.

Key words: Caudal, children, epidural, ketamine, neuroendocrine stress response

Introduction

Interest in combining regional and general anesthesia to offer the possibility of pain free post-operative period has increased in recent years.[1] Caudal block is the most commonly used regional technique for post-operative analgesia in children.[2,3] It is a reliable and safe technique that can be used with general anesthesia for intra and post-operative analgesia in children undergoing infraumbilical and lower limb surgeries.[4]

Various pharmacological agents have been used and studied as adjuvants to local anesthetic drugs in order to achieve better quality and longer duration of analgesia in the post-operative period. Of these agents, ketamine[1,5,6,7] and fentanyl[8,9] have been found to provide satisfactory analgesia in the post-operative period in children undergoing infraumbilical surgery.

It is well-known that endocrine response to surgery occurs in children as in adults.[10,11,12] Nakamura and Takasaki studied neuro-endocrine response during caudal analgesia in children and demonstrated an increase in blood insulin and cortisol levels, suppression of growth hormone, and decrease in blood glucose and catecholamine concentrations following caudal block.[13] This response has been studied and validated by other investigators[14,15,16] using morphine, ketamine and bupivacaine as caudal agents.

This study was aimed to compare ketamine and fentanyl as adjuvants in caudal block, to study their analgesic efficacy and

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effect on neuroendocrine stress response (NESR) in children undergoing infraumbilical and perineal surgery.

Materials and Methods

After obtaining approval of institutional ethics committee and written informed consent from parents of children included in the study, 60 children (2-10 years of age) undergoing infraumbilical and perineal surgery were included in this prospective, controlled, randomized and double blinded study performed according to the declaration of Helsinki.

Randomization was carried out by draw of lots. Sealed envelopes containing the group number were kept for double blinding the study.

Exclusion criteria included contraindication to caudal block, history of pre-existing neurological or spinal disease, known endocrine or neurological abnormalities or conditions likely to alter stress hormones such as preexisting pain and hypovolemia.

Three groups of children of age group 2-10 years undergoing infraumbilical and perineal surgery belonging to ASA Grade I and II were randomly assigned to receive caudal block with:

1. Bupivacaine 0.25% 1 ml/kg + 0.9% normal saline (0.1ml/kg) (wt related volume) to ensure that volume of solution injected caudally remains same in all the groups.
2. Bupivacaine 0.25% 1 ml/kg + 1 μg/kg fentanyl.
3. Bupivacaine 0.25% 1 ml/kg + 0.5 mg/kg ketamine (preservative free).

The procedure of the study including the detailed method of pain assessment and blood sampling for stress response measurement was explained to the parents/guardians as well as to the children (who could understand).

Routine pre-operative evaluation was performed and all children were premedicated with oral midazolam 0.4 mg/kg 30 min prior to induction of anesthesia. Inhalational induction using sevoflurane was done in children younger than 5 years of age and anesthesia was induced by propofol in older children. Following induction of anesthesia, an appropriate size laryngeal mask airway was placed and caudal block was given by the anesthetist conducting the case. To ensure double blind nature of study the drug was prepared by another anesthetist who gave unlabeled syringes containing bupivacaine and adjuvant to anesthetist performing the block. Anesthesia was maintained with a mixture of O_2/N_2O and sevofluranes. Intra-operative monitoring included heart rate, electrocardiogram, respiratory rate, blood pressure, Spo_2 and temperature. Reversal of anesthesia was performed as per standard protocol.

Parameters observed

1. For assessment of stress response:
   Blood samples were taken for measurement of blood glucose level by glucometer. Serum cortisol levels and serum insulin levels were measured by radioimmunoassay (through commercially available kits) at various time intervals:
   a. Just after induction as baseline value before giving caudal block (T0)
   b. 30 min after start of surgery (T30)
   c. 60 min after end of surgery (T60).
2. Assessment of post-operative pain:
   Using the modified visual analog scale (VAS) scale [Figure 1] at 0 h, 0.5 h, 1 h, 2 h, 4 h, 6 and at 24 h after surgery.
   The modified VAS scale used in this study integrates the subjective assessment by the patient using standard 10 cm line and also observational assessment by using Facies scale (for children ≤5 years).The scores were assessed by a single blinded observer at all-time intervals post-operatively. The nurses and parents were explained about the pain assessment and rescue analgesia was given whenever VAS scores were ≥3.
3. Sedation was assessed in the same time intervals as pain by using the sedation score[7,17] in which 0: Alert and awake; 1: Asleep and arousable by verbal contact; 2: Asleep and arousable by physical contact; 3: Asleep not arousable.

All children were observed for side effects of the drugs used and complications till the end of the study. This included observation for respiratory depression, nausea, vomiting, itching, urinary retention and motor weakness.

The study ended when pain score become equal to or more than 3. The rescue analgesia at this time was given in the form of paracetamol 15 mg/kg orally.

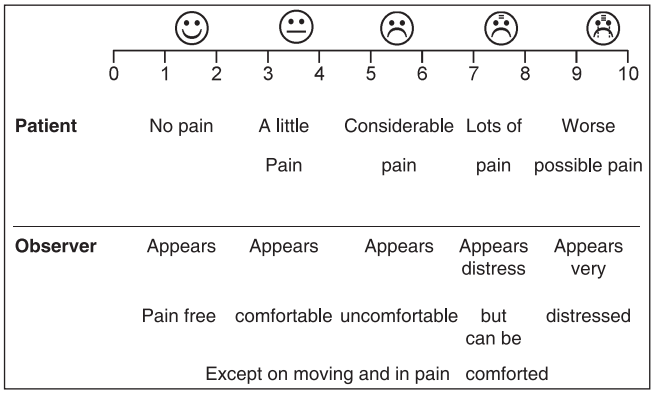

Figure 1: Modified visual analog scale

Statistical analysis

Sample size calculation: Considering $SD_1 = 0.51$ and $SD_2 = 0.72$ in the bupivacaine and ketamine groups, to study a difference of 0.65 units in mean values of VAS score at 90% power and alpha value of 5%, a sample size of 20 cases in each group was required.

Statistical analysis of data was performed by repeated measures Analysis of Variance (ANOVA) followed by Tukey's test at 5% for multiple comparisons. $P < 0.05$ was considered to be significant.

Results

The demographic profile in all the three groups was comparable [Table 1]. The average duration of surgery in all the groups was 40-45 min.

All the children underwent similar types of surgeries [Table 2].

Rescue analgesia in bupivacaine alone group was given at 4 h, therefore statistical comparison between the groups could be done only up to 4 h. Mean VAS score in bupivacaine group varied from 0.41 ± 0.51 to 2.59 ± 0.51.

Mean VAS score in Fentanyl group ranged from 0.16 ± 0.38 in immediate post- operative period to 1.74 ± 0.45 at 4 h post-operatively. At 6 h, VAS score in fentanyl group was 2.58 at which time rescue analgesia was administered.

Mean VAS score in Ketamine group varied from 0.15 ± 0.37 in immediate post-operative period to 1.25 ± 0.72 at 4 h (mean) post-operatively.

VAS score in Ketamine group was significantly lower at 0.5, 1, 2 and 4 h post-operatively when compared to Bupivacaine (I) and Fentanyl Group (II) ($P < 0.05$). VAS scores in fentanyl group were significantly lowers ($P < 0.05$) at 0, 0.5, 1, 2 and 4 h when compared to Bupivacaine group alone [Table 3].

Mean VAS scores in ketamine group at 6 h was 1.55. In this group, rescue analgesia was administered at 8 h (VAS > 3).

As all children received rescue analgesia after 8 h, VAS scores became invalid after this time period.

Mean time for requirement of rescue analgesia in bupivacaine group was 4.10 ± 0.5 h, whereas it was 5.95 ± 0.63 in fentanyl group and 8.23 ± 0.57 in ketamine group. This difference between the three groups was statistically significant ($P < 0.5$).

Table 1: Demographic profile

Group	Age (years) (mean ± SD)	Weight (kg) (mean ± SD)	Surgical duration (mean ± SD)
I	5.85±2.83	17.75±6.92	44.20±5.23
II	6.05±2.53	18.47±5.4	39.4±5.8
III	5.55±2.46	18.10±5.58	42±6.3
P value	>0.05	>0.05	>0.05

Table 2: Type of surgeries

Surgery	Group I	Group II	Group III
Herniotomy	15	16	17
Circumcision	3	2	2
Hypospadias	2	2	1

Table 3: VAS scores in all groups at various time intervals

Post-operative time (hrs)	Group I	Group II	Group III	*P* value
0	0.4±0.5*	0.1±0.3	0.1±0.3*	>0.05
0.5	0.8±0.6*	0.3±0.5	0.1±0.3*	<0.00
1	1.3±0.5*	0.7±0.6	0.40±0.5*	<0.00
2	1.7±0.5*	1.4±0.6	0.7±0.6*	<0.00
4	2.6±0.5	1.7±0.4*	1.2±0.7*	<0.00
6	NA	2.6±0.6	1.5±0.5	<0.00

**Implies significance between Group I. VAS = Visual analog scale*

Time for rescue analgesia was highest in ketamine group, indicating longer duration of post-operative analgesia with ketamine as compared to fentanyl and Bupivacaine group [Figure 2].

Patients in ketamine group were significantly more sedated than Bupivacaine group at 0.5 h post-operatively ($P < 0.05$). However, sedation scores after initial 30 min were not significantly different between the groups ($P > 0.05$) [Figure 3].

There was no evidence of other side-effects such as motor weakness, urinary retention or pruritis in any group.

NESR was assessed by measurement of blood glucose, serum cortisol and serum insulin at T0 (baseline), T30 (30 min after surgical incision) and T60 (60 min post-operatively).

Baseline values of indices were comparable within all the groups. Blood glucose increased significantly within the groups at T30 and T60, but the increase was not significant between the groups. Serum cortisol levels decreased significantly at 30 and 60 min after onset of surgery. This decrease was statistically significant ($P \leq 0.5$) within the groups, however there was no statistical significance between the groups. A similar trend was observed with serum insulin. The values

for serum cortisol and serum insulin were lowest in ketamine group [Table 4] [Figure 3].

Discussion

Caudal block is a well-accepted technique for achieving intraoperative and postoperative pain relief in lower abdominal surgeries in children. Prolongation of caudal analgesia has been achieved by the addition of various adjuvants such as fentanyl, ketamine and clonidine with bupivacaine.[5,6,7,8]

The optimum dosages of fentanyl and ketamine used caudally by previous workers were 1 μg/kg and 0.5 mg/kg respectively.[5,9] A study by Constant *et al.*[8] concluded that caudal fentanyl in a dose of 1 μg/kg provided satisfactory analgesia of longer duration with negligible respiratory depression. Semple *et al.*[5] reported that caudal ketamine in a dose of 0.5 mg/kg when used as adjuvant caused effective analgesia with minimal behavioural disturbances in children. We used similar dosages in our study.

We used already established methods for pain assessment — viz., modified VAS score, and serum cortisol, serum insulin and blood glucose levels as indicators of stress response in accordance with studies conducted by other workers.

The results of the present study confirm and support previous reports that caudal administration of ketamine and fentanyl exert modulatory influences on post-operative pain mechanisms. We achieved good pain relief with very low VAS scores in all the three groups in immediate post-operative period. However, in children who received bupivacaine alone, we found that rescue analgesia was required at a much earlier time, approximately 4 h as compared to 8 h in ketamine and 6 h in fentanyl group.

This finding is in agreement with previous studies by Martindale *et al.*[17] Naguib *et al.*[7] and Lonnquist.[18]

Patients receiving Fentanyl showed significantly lower VAS scores as compared to bupivacaine until 4 h post-operatively indicating a better quality of analgesia with fentanyl.

Our results are comparable to those of Constant *et al.*[8] and Desai *et al.*[9] who concluded that duration of analgesia with fentanyl 1 μg/kg as adjuvant was 5.04 ± 0.35 h and 4.21 ± 1.75 h respectively. In our study, duration of analgesia with Fentanyl was 5.95 ± 0.63 hrs.

With ketamine added to Bupivacaine, VAS scores were lowest when compared to bupivacaine alone and bupivacaine with fentanyl at all-time points. This difference was statistically significant up to 4 h post-operatively. Rescue analgesia in this group was required at 8 hrs. post-operatively.

Several studies have shown a longer duration of analgesia with ketamine when used as adjuvant with caudal block in children. Semple *et al.*[5] and Cook *et al.*[19] demonstrated

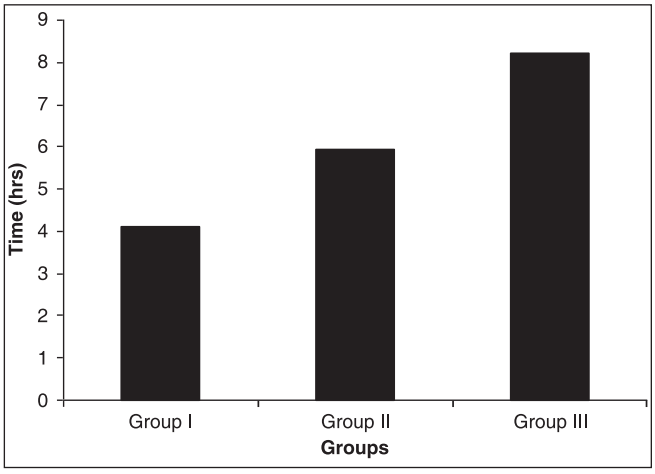

Figure 2: Time to rescue analgesia

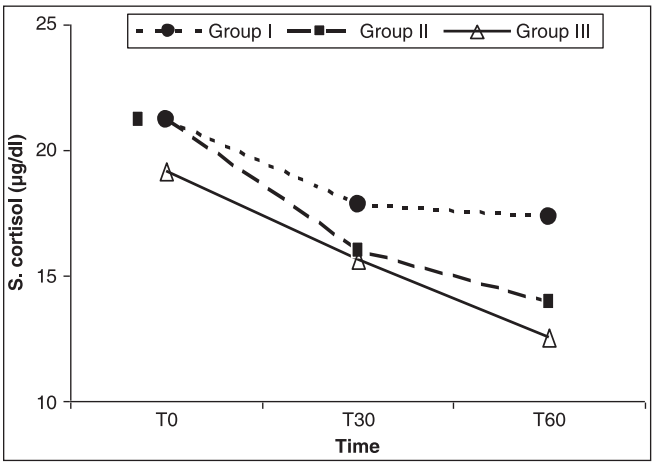

Figure 3: Serum cortisol level

Table 4: Stress response parameters in all three groups at various time intervals (mean ± SD)

Time	Blood glucose (mg/dl)			Serum cortisol (μg/dl)			Serum insulin (μIU/ml)		
	Group I	Group II	Group III	Group I	Group II	Group III	Group I	Group II	Group III
T 0	84.30±5.78	84.11±6.78	84.75±5.57	21.18±3.74	21.21±4.05	19.13±4.63	12.42±5.58	10.92±5.09	7.62±5.24
T 30	93.25±7.59*	92.26±7.82*	90.80±6.26*	17.85±5.26*	16±4.09*	15.60±4.98*	7.73±4.77*	7.67±4.88*	5.88±4.16*
T 60	100.35±7.2*	97±8.28*	95.55±6.22*	17.33±6.88*	13.92±6.43*	12.55±5.34*	7.28±4.38*	5.93±4.05*	5.14±3.70*

**Implies significance within the groups, P < 0.05. SD = Standard deviation*

that caudal ketamine provided a longer median duration of analgesia. Our study confirms that ketamine in a dose of 0.5 mg/kg as adjuvant provides longer duration and better quality of analgesia when compared to bupivacaine alone and bupivacaine with fentanyl, with no incidence of motor weakness or urinary retention.

Patients in ketamine group were significantly more sedated as compared to the other two groups. However, this sedation was seen only up to 30 min post-operatively. This finding is consistent with that of Martindale SJ *et al*.[17] who also documented similar findings in their study. Campbell *et al*.[20] noted no difference in sedation scores between patients receiving caudal bupivacaine and bupivacaine-fentanyl mixture which is in corroboration with our findings.

With bupivacaine alone, glucose concentration increased significantly at 30 min after surgical incision and 60 min post-operatively from baseline values in all three groups. However this increase in blood glucose was not significant between the groups. Akbas *et al*.[1] reported comparable increase in blood glucose levels in both groups of patients receiving ketamine or bupivacaine and concluded that addition of ketamine has no further advantage over caudal analgesia with bupivacaine alone in suppressing hyperglycemic response to surgery.[1] Tuncer *et al*.[22] measured glucose concentration in children who received caudal or general anesthesia. In both groups glucose concentration increased, however glucose concentration was lower in caudal group than control group. In our study blood glucose was significantly increased in all three groups though the values were within normal range. This may be due to hepatic glycogenolysis, gluconeogenesis and insulin resistance at cellular level. Thus normal regulation of glucose homeostasis is ineffective peri-operatively and hyperglycemia is inevitable.

Serum cortisol levels on the other hand, decreased significantly within the groups in all three groups. However, there was no statistical significance between the groups. This is in agreement with the findings of Murat *et al* [21] Nakamura and Takasaki [13] and Tuncer *et al*.[22] who concluded that epidural anesthesia blocks afferent neurogenic impulses from the site of surgery and hence reduces the cortisol response to surgery in children during the first 24 h as compared to general anesthesia alone Similar study carried out by these authors on comparison between clonidine and ketamine added to ropivacaine caudally, on stress hormone levels, found that cortisol levels were reduced in all the groups and opined that there was no added effect of clonidine or ketamine in modifying the stress response.[1]

We found that serum insulin values decreased significantly within the group in all three groups, though, there was no statistical significance between the groups throughout the study period.

In a study conducted by Nakamura and Takasaki,[13] plasma insulin concentration remained unchanged in the caudal group in children. They suggested that insulin secretion during surgery is suppressed by the direct effect of anesthesia and by activation of the sympathetic nervous system. They stated that this may have resulted from moderate and constant levels of plasma glucose and catecholamines during surgery.

Our observations are similar to that of Tuncer *et al*.[22] wherein insulin levels remained lower following caudal block, though in our study all children received caudal block with general anesthesia.

Thus, from the results of our study we can conclude that ketamine at a dose of 0.5 mg/kg when used as an adjuvant to bupivacaine is better than fentanyl 1 μg/kg in terms of analgesia as well as blunting of stress response.

Limitation of the study

The patient profile of our study makes it difficult to distinguish between sedation and analgesia as a pain free child is comfortable and asleep. According to Beyer *et al*, self-reporting and behavioral pain measures may be discordant in children between 3 and 7 years of age.[23]

As the power calculation of the study was based on a difference in analgesia, the difference in stress response may be better highlighted in a larger study. This study can thus serve as a pilot study to indicate difference in stress response by addition of an adjuvant like ketamine and fentanyl to caudal bupivacaine.

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