Original Article

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Comparison of Efficacy of Caudal Clonidine in Two Different Dosages with Ropivacaine on Neuroendocrine Stress Response to Surgery in Children Undergoing Lower Abdominal and Urological Surgeries Under General Anaesthesia

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Abstract

Background: Neuroedocrine stress response(NESR) to surgery is manifested by increase in circulating catabolic hormones (cortisol) leading to protein catabolism. This can be modified by providing adequate postoperative analgesia in children in the form of caudal block using ropivacaine and non opioid adjuvants like clonidine.There is paucity of literature comparing effects of 3µg/kg and 1.5µg/kg of clonidine with 0.2% ropivacaine in terms of neuroendocrine stress response to surgery in caudal block. *Methods:* 45 children aged 1- 8 years, after premedication with oral midazolam and induction of anesthesia, caudal block was performed. Children were randomly allocated into 3 groups. Blood samples were obtained just after induction of anesthesia, 30 minutes after the start of surgery and 60 minutes after the end of surgery for measurement of serum levels of glucose and cortisol. *Results:* Mean blood glucose were within normal range and there was no statistically significant difference between the groups. There was a significant rise in serum cortisol levels from baseline values (T_0) in group R in the post operative period. There was statistically significant fall from baseline levels in cortisol values postoperatively in the clonidine 1.5 µg/kg group(RC1.5) and clonidine 3µg/kg group (RC3) and this fall in cortisol values was greater in the clonidine 3µg/kg group when compared to the clonidine 1.5 µg/kg group. *Conclusions:* There was blunting of NESR to surgery when clonidine was used as adjuvant to ropivacaine in caudal block and this was maximum with clonidine dosage of 3µg/kg.

Keywords: Neuroendocrine Stress Response; Clonidine; Ropivacaine; Caudal Block.

Introduction

Neuroendocrine stress response is a well established response to surgical and anaesthetic interventions manifested by increase in sympathetic tone, increase in circulating catecholamines and catabolic hormones (cortisol, ADH, ACTH, aldosterone, rennin angiotensin) [1]. This leads to increased oxygen consumption and protein catabolism which may impede recovery. Caudal anaesthesia provides satisfactory postoperative analgesia, reduces the amount of inhaled or intravenous anesthetic administration, facilitates a smooth and rapid recovery and attenuates stress responses to surgery [2,3].

In order to increase the success and overcome the unwanted side effects of local anaesthetics when used alone, different drug combinations in the form of adjuvants have been tried. These include opioids like morphine and fentanyl and non-opioids like α_2 adrenergic agonists clonidine, ketamine, epinephrine and neostigmine [4].

Clonidine among these, has in recent years emerged as a popular adjuvant has lesser side effects like respiratory depression, nausea and vomiting when compared to opioids. It has been used in dosages of 1.5 and 2 µg/kg [5]. Ivani et al [6] used 2 µg/kg of clonidine with caudal ropivacaine and reported it to be efficacious without causing adverse haemodynamic changes and sedation. A higher dosage of 5 µg/kg has been shown to be associated with adverse effects of sedation and bradycardia by Motsch et al [7]. There is paucity of literature to show comparison of effects of 3µg/kg and 1.5µg/kg on neuroendocrine stress response to surgery.

Thus, this study was designed with the aim to assess and

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compare efficacy of two different dosages of clonidine (1.5μg/kg and 3μg/kg) when used as adjuvant with 0.2% ropivacaine in single shot caudal epidural block in children on neuroendocrine stress response to surgery.

Methods

The study was conducted in the Department of Anaesthesiology and Critical Care at University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi after approval from institutional review board. The procedure of the study including blood sampling for stress response measurement was explained to the parents / guardians and to the children (who could understand). Informed written consent was obtained from the parents of children included in the study.

Study Design

The study design was prospective, controlled, randomized and double blind. Randomization was performed by computer generated randomization code and delivered in sealed, opaque, sequentially numbered envelopes. The number of patients required in each group was determined according to data obtained from previous studies. According to this hypothesis, a sample size of 15 patients in each group was adequate with alpha risk of 0.05 and a power of 0.8.

Patient Selection

Three groups of children of age group 1-8 years undergoing elective lower abdominal and urological surgeries with average duration of 90 minutes belonging to ASA grade I and II were randomized to receive caudal block after induction of general anaesthesia as follows:

- Group R: Ropivacaine 0.2% (1 ml/kg) + 0.9% normal saline (0.1 ml/kg) (weight related volume) to ensure that volume of solution injected remains same in all the study groups
- Group RC1.5: Ropivacaine 0.2% (1 ml/kg) + clonidine 1.5 μg/kg
- Group RC3: Ropivacaine 0.2% (1 ml/kg) + clonidine 3.0 μg/kg

It was ensured that the upper limit of dose of ropivacaine, which is 2 mg/kg, is not exceeded in any of the subjects. Drugs were prepared by an anaesthesiologist before induction of anaesthesia, leaving the observer unaware of the group assigned.

Exclusion Criteria

- History of allergy to local anaesthetics or clonidine.
- History of coagulation abnormalities.
- History of aspirin ingestion in the preceding week.
- History of pre-existing neurological or spinal disease.
- Patients with known endocrine abnormalities.
- Patients with conditions which are likely to alter stress hormones such as hypovolemia and preexisting pain.
- History of ingestion of any drug which has depressant effects on central nervous system or cardiovascular system.

Anaesthesia Technique

A standard anaesthesia technique was followed in all children included in the study. Routine preoperative evaluation was performed on all children. After conducting a thorough pre-operative check up to ensure adherence to our exclusion criteria, children were premedicated with oral midazolam syrup(0.4 mg/kg) 30 minutes prior to induction of anaesthesia. After receiving the patient in the operation theatre, routine monitoring was established and anaesthesia was induced with 6-8% sevoflurane in oxygen using a face mask.

After the child was adequately anaesthetized, intravenous access with appropriate size IV cannula was obtained. An appropriate sized laryngeal mask airway was placed. The patient was allowed to breath spontaneously via an Ayre's T piece (with Jackson Rees modification) breathing system. Anaesthesia was maintained with a mixture of 40% oxygen in nitrous oxide and isoflurane 0.5-1.0%. The child was then positioned in lateral position and caudal block was performed by a skilled anaesthetist or resident under the supervision of consultant anaesthesiologist using aseptic technique and a short bevelled 22-23G needle. After negative aspiration of blood and CSF, the study drug was injected according to the group assigned as per the randomization code. The anaesthesiologist involved in the study was blinded to the contents of the syringes containing the study medications.

Standard monitoring included non-invasive blood pressure (by oscillometry), ECG, heart rate, pulse

oximetry, end tidal carbon dioxide, respiratory rate and temperature. These parameters were monitored at the time of induction and at 5 minute intervals thereafter. An intraoperative rise in baseline arterial pressure or heart rate of >10% after surgical incision was taken as an indicator to insufficient anaesthetic depth and concentration of inhalational agent was increased. If there was persistent rise in heart rate and blood pressure for more than 10 minutes, then failure of caudal block was presumed and rescue analgesia in the form of opioids (fentanyl 1 µg/kg IV) was injected and the patient was excluded from the study.

At the end of surgery, the laryngeal mask airway was removed and the child was shifted to post-anaesthesia care unit (PACU). All children had at least one parent / guardian in attendance during recovery. One blinded observer recorded all the data in PACU.

1. Blood samples were taken :
   a) Just after induction as baseline value before giving caudal block
   b) 30 minutes after start of surgery
   c) 60 minutes after end of surgery

Samples were Analysed for

- Measurement of blood glucose by glucometer.
- Serum cortisol levels measured by radio-immunoassay (through commercially available kits).

Approximately 5-6 ml of blood was drawn from a dedicated vein cannulated with 22 G IV cannula.

2. All children were observed for side effects of drugs used and complications till the end of the study. This included observations for sedation, respiratory depression, nausea and vomiting, urinary retention, hypotension and bradycardia. The sedation in the postoperative period was assessed by a scoring system as follows:

Sedation Score [15]

0 Awake and alert

1 Asleep, arousable by verbal contact

2 Asleep, arousable by physical contact

3 Asleep, not arousable

Statistical Analysis

Data was analysed using SPSS version 17 computer software. Student's t-test was used for significance and $p<0.05$ was taken as significant. The comparison of sedation scores between the 3 groups was done using non parametric tests - Mann Whitney test and Kruskal Wallis test Inter group comparisons for blood glucose and serum cortisol levels was done using multivariate tests.

Results

Neuroendocrine Stress Response (NESR)

NESR was assessed by measurement of blood glucose and serum cortisol at T_0 (baseline), T_{30} (thirty minutes after surgical incision) and T_{60} (sixty minutes post operatively)

Blood glucose (mg/dl)

Mean blood glucose at T_0 (baseline) was 89.93 ± 13.776 in group R, 91.07 ± 16.62 in group RC1.5 and 92.53 ± 13.23 in group RC3. These values were within normal range and there was no statistically significant difference between the groups ($p>0.05$).

The mean blood glucose levels in groups R increased above baseline values(89.93) at T_{30} - thirty minutes after surgical incision (95.6)and a fall in blood glucose levels was noticed postoperatively – T_{60} (91.73) when compared to introperative values, but this difference was not statistically significant.

The blood glucose values in group RC1.5 increased above baseline levels(91.07) both intraoperatively (T_{30} – 95.67) and post operatively.(T_{60} – 96.33). The post operative values were higher than intraoperative blood glucose levels but this was not significant statistically.

In group RC3, an increase in blood glucose levels was noted introperatively - T_{30} (94.27) when compared to baseline levels.(94.27). the blood glucose values decreased postoperatively – T_{60} (89.6) when compared to intraoperativ and baseline values. This was also not significant statistically.

Thus, although the blood glucose values at T_{30} and T_{60} were highest in group R and lowest in group RC3, this difference was not statistically significant.The trend in the blood glucose levels at T_{30} and T_{60} were lowest in RC3 group.

Serum Cortisol (µg/dl)

The mean serum cortisol at T_0 was 10.36 ± 6.13 in group R, 7.60 ± 3.96 in group RC1.5 and 10.53 ± 4.54 in group RC3. All the groups had comparable serum

cortisol levels at baseline and this was within the normal range in all the groups.

T_{30}

30 minutes after surgical incision (T_{30}) groups R and RC3 showed a fall in serum cortisol levels which were 7.2 ± 3.99 and 6.25± 3.71 respectively. The values in RC1.5 (7.74 ± 3.66) were similar to baseline cortisol levels.The change of serum cortisol levels in groups R and RC3 was statistically significant when compared baseline (T_0) values. However all the values were within normal range for the age group studied.

T_{60}

At T_{60} -- the serum cortisol levels in group R(17.5 ± 5.78) increased significantly when compared to baseline and intraoperative levels. In group RC1.5, the postoperative values(6.85 ± 3.37) decreased when compared to intraoperative and baseline levels. In group RC3, no further fall was noticed postoperatively and the values were similar to intraoperative values, however this value was significantly less when compared to baseline

Thus, there was a significant rise in serum cortisol levels from baseline values (T_0) in group R in the post operative period. There was statistically significant fall from baseline levels in cortisol values postoperatively in RC1.5 and RC3 group and this fall in cortisol values was greater in the clonidine 3µg/kg group when compared to the clonidine 1.5µg/kg group.

Side Effect Profile

Sedation Score

The patients in group RC3 and RC1.5 were significantly more sedated when compared to group R in the immediate post operative period, but were arousable within 30 minutes postoperatively. There was no significant difference in sedation between group RC 1.5 and RC3 till 1hour post operatively.

All children who received only ropivacaine were awake and alert within 30 minutes after completion of surgery. Sedation persisted till 2 hours postoperatively in children who received clonidine with ropivacaine, but all children were awake and alert by 4 hours. postoperatively. The difference in sedation between children who received 1.5µg/kg and 3µg/kg of clonidine was not significant statistically and clinically.

Table 1: Demographic profile

Group	R	RC 1.5	RC 3
Age (years) (mean ± SD)	5.9 ± 1.94	5.7 ± 2.37	5.9 ± 1.94
Surgical duration (minutes) (mean ± SD)	46.06± 13.50	47.66 ± 12.79	46.26 ± 11.51
Males/ Females	14/1	14/1	14/1

Table 2: Mean blood glucose levels in all groups at different time intervals (mg/dl)

Time	Group R	Group RC1.5	Group RC3
T_0	89.93 ± 13.77	91.07 ± 16.62	92.53 ±13.23
T_{30}	95.60 ± 12.40	95.67 ± 13.069	94.27 ± 16.224
T_{60}	91.73 ± 10.38	96.33 ± 11.22	89.60 ± 14.94

Table 3: Serum cortisol levels in all three groups at various time intervals (µg/dl)

Time	Group R	GROUP RC1.5	GROUP RC3
T_0	10.36 ± 6.13	7.60 ± 3.96	10.53 ± 4.54
T_{30}	7.2 ± 3.99	7.74 ± 3.66	6.25± 3.71
T_{60}	17.5± 5.78	6.85 ± 3.37	6.75 ± 4.35

Table 4: Sedation Score in all 3 groups at various time intervals

Postoperative Time (hrs)	Group R	Group RC1.5	Group RC3
0	1.8 ± 0.56	3 ± 0.0	2.86 ± 0.35**,
0.5	0.6 ± 0.63	2.33 ± 0.48*	2.4 ± 0.82**,
1	0.0 ± 0.0	1.53 ± 0.63*	1.26 ± 0.79**,
2	0.00 ± 0.00	0.3 ± 0.49	0.58 ± 0.79**,
4	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

*Significant difference between group R & RC1.5 (P value ≤ 0.05);
** Significant difference between group R &RC 3(P value ≤ 0.05);

Discussion

Neuroendocrine Stress Response (Nesr)

Attenuation of NESR by various drugs and techniques has been a recent area of research interest. The most frequent markers used to assess NESR are serum cortisol and blood glucose levels.

Although many drugs have been extensively reviewed to modulate NESR, very few studies are available to study the effect of caudal clonidine with ropivacaine for the same in the paediatric age group. M Akbas et al [8] studied the effect of clonidine on NESR in a dose of 1µg/kg with ropivacaine in caudal block, and compared it to ketamine as adjuvant to ropivacaine. These authors reported a blunting of NESR as depicted by a decrease in blood glucose and serum cortisol levels and an increase in insulin levels. We compared 1.5 µg/kg and 3 µg/kg clonidine with ropivacaine in caudal block.

We did not take blood samples preoperatively for hormonal levels because changes in these are likely to occur in emotionally stimulated children preoperatively, especially in older ones who feared operation or had separation anxiety. Hence a baseline sample was taken immediately after induction but before administering caudal block.

The baseline values (T_0) for all the markers were within the normal ranges for children in this age group (cortisol 3.3 – 20.8 µg/dL, glucose 65 – 125 mg/dL).There were no differences amongst the three groups in the cortisol and glucose values measured before the start of surgery.

Blood Glucose

Normally, a rise in blood glucose levels is observed peroperatively and may be explained by hepatic glycogenolysis, gluconeogenesis and insulin resistance at cellular level that takes place perioperatively. Thus normal regulation of glucose homeostasis is ineffective perioperatively and hyperglycemia is inevitable.

In our study too, a rise in blood glucose levels perioperatively was found to occur in all the study groups although the values remained within normal range for that subset of population.

Earlier studies comparing caudal block with General Anaesthesia(GA) alone group have reported a reduction in the NESR in caudal group as opposed to GA alone [9].

Tuncer et al measured glucose concentration in children who received either caudal with GA or GA alone. In both groups glucose concentration increased above baseline values, however this increase was lower in caudal group when compared to in control group (G A alone) [9] .

M Akbas et al reported a suppression of NESR with ropivacaine [10]. In another study, a greater blunting of stress response was noted by the same authors when clonidine in a dose of 1µg/kg was used as adjuvant. They compared the suppression of NESR by clonidine with that of ketamine when used as adjuvant to ropivacaine. The findings of this study indicated a greater blunting of NESR with clonidine as depicted by decrease in glucose and cortisol levels and increase in insulin levels [8].

Although we did not have a control group comprising only GA group (without any caudal block), the fact that all blood glucose values were within normal range may indicate a blunting of NESR in all the three groups. This beneficial effect was found to be maximum with clonidine 3µg/kg group (children in clonidine 3µg/kg group had lowest blood glucose levels in the post operative period).

Serum Cortisol

The baseline cortisol values were comparable in all the 3 groups and the mean value ranged between 7.6 and 10.53µg/dl. The values at 30min following surgical incision were similar to baseline values in ropivacaine only group and ropivacaine with clonidine 1.5µg/kg group, but a significant decrease in cortisol levels at 30 minutes was noticed in children receiving clonidine 3µg/kg with ropivacaine.

The trends in children who received ropivacaine with clonidine 1.5µg/kg group showed a slight rise intraoperatively as against a fall in cortisol levels with the other two groups. We are unable to provide a suitable explanation for the same. A larger study group is probably required to seek further information in this regard.

There was a modest fall in the serum cortisol values postoperatively in clonidine1.5µg/kg group and a significant fall in clonidine 3µg/kg group as against a significant rise in serum cortisol levels in ropivacaine only group (albeit within normal range). These trends signify significant blunting of NESR with clonidine.

According to Nicholson G et al, serum cortisol levels begin to rise within minutes of surgical incision and reach maximum values upto 4 – 6 hours postoperatively [11].

Solak et al [12] assessed the effects of caudal analgesia with 0.25% bupivacaine in addition to general anesthesia on plasma cortisol and prolactin concentrations during the early postoperative period in children who underwent abdominal and genitourinary surgery. They found low-pain scores and lower hormone concentrations in the general anesthesia plus caudal analgesia group than general anesthesia alone.

A review article by Desborough et al [13] have shown that clonidine reduces the stress response to surgery. The results of our study correlates well with the above mention facts and suppression of NESR is seen to be significant with clonidine in a dosage of 3µg/kg.

Murat and co workers[14]demonstrated that epidural anaesthesia reduces the cortisol response to surgery in children 1 to 8 year old during the first 24 hours after lower abdominal or perineal surgery. Cortisol values decreased significantly at the end of surgery in caudal epidural group while the patients who received GA alone had increased cortisol values. Throughout the study all cortisol values remained at a significantly lower level in the caudal group than in the control group. This finding is in agreement with our study where cortisol levels remained at lower values in the postoperative period. This is explained by the fact that the decrease in stress response is due to complete blockade of afferent neurogenic impulses from the site of surgery.

Our findings, therefore, clearly indicate a modulation of NESR with caudal clonidine and a significant reduction of stress response with clonidine in a dosage of 3µg/kg.

Conclusions

Both dosages of clonidine (1.5 and 3µg/kg) were effective in blunting NESR. The effect was significantly higher with clonidine 3µg/kg.

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