

Anaesthesia and the Acute Phase Protein Response in Children Undergoing Circumcision

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Concentrations of acute phase proteins (CRP: C-reactive protein, albumin) change during surgery. We investigated the acute phase response to circumcision and the effects of anaesthesia on this response. The children were divided into four groups; group 1 (intratracheal general anaesthesia, $n = 40$), group 2 (general anaesthesia with mask, $n = 20$), group 3 (ketamine, $n = 20$), group 4 (local anaesthesia, $n = 35$). Blood samples were obtained, 24 hours before circumcision, after premedication, and 24 hours after circumcision. CRP and albumin before circumcision were comparable for all groups. There was no increase in CRP, and albumin remained steady throughout the study. No difference was observed among the groups, and related to anaesthesia. No responsiveness may be explained with the size of injured tissue or anatomical and histological type of preputium.

INTRODUCTION

Cytokines are the mediators of the physiological response to surgical trauma. The cytokine response to surgery involves inflammation, immune and pituitary hormonal responses, hematopoiesis, and tissue repair. The major cytokine synthesized after surgery is interleukin-6 and this stimulates acute phase protein (APP) synthesis in the liver. Concentrations of APPs rise significantly during acute inflammation owing to surgery, myocardial infarction, infections, and tumors [1, 2, 3, 4].

C-reactive protein (CRP) is one of the plasma acute phase proteins with the largest and earliest rise. Increase in the synthesis of APPs is accompanied by a decrease in the synthesis of some proteins called negative APP. Albumin (Alb) is a negative APP and albumin values fall in the presence of inflammatory cytokines [1, 3].

Except for ritual circumcision, boys are circumcised because of medical indications such as recurrent balanitis, severe phimosis, and paraphimosis. Circumcision prevents urinary tract infections, reduces the incidence of penile carcinoma, also reduces the spread of HIV and other sexually transmitted diseases [5, 6, 7]. Researches related to circumcision have increased for these reasons.

Some physicians performing circumcision without any form of analgesia, believe that neonates do not feel or remember pain [8], but local anaesthesia including topical application of cream, emulsion or gel, or dorsal penile nerve block, and penile ring block are recommended for neonatal circumcision [5, 9]. Regional anaesthetic techniques like caudal epidural block, are useful for circumcision [10]. Although circumcision can be performed under local anaesthesia even in older boys, general anaesthesia is required in children older than six months of age [6].

In our society, circumcision is performed as day case surgery, generally under local anaesthesia. The parents choose the anaesthesia type but at the departments of pediatric surgery, general anaesthesia is preferred.

There are several studies reporting the effects of the type of anaesthesia on acute phase response [2, 3, 11, 12]. The concentrations of APPs in children change after major [13] and minor surgery [14]. Khilnani et al hypothesized that children have a different stress response to surgery than adults and they found that hormonal responses to surgical stress in children were not affected by age, length of surgery, and anaesthetic technique [15]. To our knowledge acute phase response (CRP and albumin) to circumcision has not been previously studied. The purpose of this study was to confirm the acute phase protein response to circumcision and investigate the effects of anaesthesia on this response.

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TABLE 1. Children profile (age, weight), operation time, C-reactive protein (CRP), and albumin values. Data are mean (SD).

| | Group 1 (<i>n</i> = 40) (Intratracheal general anaesthesia) | Group 2 (<i>n</i> = 20) (General anaesthesia with mask) | Group 3 (<i>n</i> = 20) (Intravenous anaesthesia with ketamine) | Group 4 (<i>n</i> = 35) (Local anaesthesia) |
|----------------------|-----------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------|
| Age (y) | 7.2 (2.8) | 7.3 (1.7) | 7.4 (1.8) | 7.1 (2.7) |
| Weight (kg) | 21.8 (7.7) | 20.8 (6.2) | 22.3 (5.9) | 23 (7.6) |
| Operation time (min) | 39.4 (12.2) | 37.9 (11) | 37.6 (9.5) | 37.9 (12.2) |
| CRP (mg/dL) | | | | |
| Sample 1 | 0.08 (0.05) | 0.09 (0.06) | 0.10 (0.06) | 0.09 (0.04) |
| Sample 2 | 0.10 (0.09) | 0.09 (0.05) | 0.11 (0.09) | 0.09 (0.05) |
| Sample 3 | 0.09 (0.05) | 0.08 (0.04) | 0.11 (0.09) | 0.08 (0.03) |
| Albumin (g/dL) | | | | |
| Sample 1 | 4.69 (0.19) | 4.70 (0.33) | 4.78 (0.39) | 4.78 (0.25) |
| Sample 2 | 4.68 (0.38) | 4.66 (0.16) | 4.72 (0.45) | 4.82 (0.28) |
| Sample 3 | 4.71 (0.20) | 4.73 (0.29) | 4.80 (0.37) | 4.80 (0.28) |

MATERIAL AND METHODS

We obtained Local Hospital Ethics Committee approval and written informed consent from the parents of 115 children, aged 1 to 13 years. Children with malnutrition, suspected infection, or chronic inflammatory conditions and receiving medications known to interfere with stress response were excluded.

After 6 hours fasting all patients were premedicated with midazolam 0.1 mg/kg intramuscularly or 0.3 mg/kg rectally and monitored via electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry (Cardio-cap/5, Datex Ohmeda, Louisville, Colo, USA) during the operation.

The patients were divided into four groups. The type of anaesthesia was determined according to the parents and the surgeons' preference. The children in group 1 (ITGA: intratracheal general anaesthesia, *n* = 40) received sevoflurane 2% via mask, fentanyl 1 µg/kg intravenously (IV) for induction, and rocuronium bromide 0.5 mg/kg IV was given as muscle relaxant. After endotracheal intubation, 50% nitrous oxide in oxygen with 2% sevoflurane was used for maintenance. In group 2 (general anaesthesia with mask, *n* = 20), children received 50% nitrous oxide in oxygen with sevoflurane 2%-3% via mask and fentanyl 1 µg/kg IV. Ketamine 1-2 mg/kg IV was used in group 3 (intravenous anaesthesia with ketamine, *n* = 20). In group 4 (local anaesthesia, *n* = 35), dorsal penile nerve block or penile ring block (1-2 or 2-4 mL of lidocaine 20 mg/mL and epinephrine 0.0125 mg/mL, subcutaneously) was used for circumcision.

Technique of sleeve circumcision [16] was performed in all children. The redundant penile and preputial skin were reduced over glans. The skin was retracted. The distal incision was marked and created carrying sharply down to Buck's fascia. After frenuloplasty, the proximal incision

was marked and carried down deeply into the dartos fascia. The sleeve of tissue was divided in the midline and the redundant tissue was excised.

Blood samples for protein analysis were obtained by venipuncture from children 24 hours before circumcision during preoperative evaluation (sample 1), on admission to hospital, after premedication (sample 2), and 24 hours after circumcision (sample 3). Three mL of blood were centrifuged, serum collected and stored at -20°C until assayed. Serum CRP and albumin values were determined by immunoturbidimetric and colorimetric methods, respectively, with Sigma kits (Sigma Diagnostics, Fla, USA) using Hitachi 717 Auto Analyzer (Boehringer Mannheim, Germany). CRP detection limit was 0.05 mg/dL. CRP concentrations remained inferior to the detection limit of assay used were accepted as zero.

Statistical analysis was performed using the SPSS for Windows 10.0 statistical programme. The parameters among the four groups were compared by ANOVA test (a value of *P* < .05 was considered as significant). The differences in the values of CRP and albumin during the study were analyzed with repeated measures ANOVA. Statistical significance was considered at *P* < .05. Results were given as mean (SD).

RESULTS

There were no significant differences in children profile (age, weight) and operation time among the groups (Table 1).

CRP values before surgery (samples 1 and 2) were comparable for all groups. In group 1 (ITGA), CRP increased on admission, and decreased after circumcision but the changes were not significant. There was a little increase of samples 2 and 3 of CRP in group 3 (ketamine) (*P* > .05). In group 2 (mask) and group 4 (local anaesthesia), the same CRP values were obtained before surgery.

We observed no increase in CRP values after circumcision in four groups (Table 1).

The albumin values 24 hours before surgery (sample 1) and on admission (sample 2) were similar for all groups, and the values remained steady throughout the study. The values did not change significantly, after circumcision. No difference was found among the groups (Table 1).

DISCUSSION

The common age period of cultural circumcision is 1 to 8 years, in our country. Although circumcision is usually performed under local anesthesia including dorsal penile nerve block or penile ring block and topical anesthesia, pediatric surgeons prefer general anaesthesia.

During cytokine response to surgery, acute phase proteins, including CRP, are synthesized in the liver, but plasma concentrations of some visceral proteins such as albumin, termed the negative phase reactant, decrease, because of alteration in synthesis rate or increased catabolism [1, 3].

The effects of anaesthesia on acute phase response to surgery have been studied in adults. It was found that the cytokine production in cardiac surgery was not affected by type of anaesthesia, thoracic analgesia combined with inhalation anaesthesia or high dose opioid anaesthesia [11]. In this study, types of anaesthesia (general or ketamine) did not affect the response. We obtained similar results in our previous study investigating the effects of anaesthetic techniques and delivery types on CRP and albumin values during uncomplicated delivery. No influence of anaesthetic techniques was found except haemodilution due to volume loading in regional anaesthesia. The type of delivery seemed to be more important than anaesthesia [17].

Eleven proteins were studied by Simpson et al, to investigate the influences of halothane and different doses of fentanyl (2-3 and 12 $\mu\text{g}/\text{kg}$) on acute phase response to elective cholecystectomy [12]. The concentration of only two proteins, fibrinogen and antichymotrypsin increased. They could not find any evidence of variation in stress suppression related to anaesthesia. The supplementation of isoflurane anaesthesia with different doses of fentanyl (3 and 15 $\mu\text{g}/\text{kg}$) did not modify the cytokine response to abdominal hysterectomy. CRP increased after 24 hours, but there was no significant difference between the groups [4]. In our study, the children in group 1 (ITGA) and group 2 (mask) received sevoflurane anaesthesia with fentanyl (1 $\mu\text{g}/\text{kg}$). We did not observe any difference in CRP and Alb as acute phase protein response to circumcision, between these groups and the other groups.

Bourguignat et al suggested that there was incomplete or absent acute phase response in some postoperative patients [18]. There was no increase of CRP after osteosynthesis in their 5 of 74 patients. These five patients had no hepatic insufficiency or protein malnutrition, and no infection was observed during the survey period. They interpreted the results as an apparent lack of CRP response

because of the limit of detection of the assay. In their study and our study, CRP detection limit was 0.05 mg/dL and CRP concentrations (< 0.05 mg/dL) were undetectable.

Preoperative fear, anxiety, starvation, length, and type of surgery and premedication are the factors affecting the hormonal response [15]. We used the same premedication (midazolam 0.1 mg/kg intramuscularly or 0.3 mg/kg rectally) for all children and there was no difference in the length and type of surgery. No change was observed between the values 24 hours before surgery (sample 1) and on admission to hospital (sample 2). We think that adequate preoperative sedation with midazolam may prevent acute phase response, by decreasing preoperative fear and anxiety. Midazolam is a short-acting benzodiazepine, also anxiolytic and hypnotic. The doses we have used provide good sedation and make the children drowsy or sleepy [19].

Booker et al showed that most infants had an increase in alfa-1 acid glycoprotein (AAG) in response to major surgical trauma [13]. The type of surgery in our study may be the reason of observing no significant changes in preoperative and postoperative values of CRP and albumin. Circumcision is not a major surgery, but in an earlier study, acute phase changes were observed in children recovering from minor surgery (inguinal hernia, undescended testis) [14]. CRP and AAG increased one day after operation. In that study there was no difference in albumin values on postoperative days when compared with preoperative values. It was concluded that prognostic inflammatory and nutritional index (PINI) was more valuable for monitoring stress response.

In our study, there was no child circumcised without analgesia. A physiologic stress including increases in heart rate and blood pressure can be reduced if analgesia is employed and local anaesthesia can relieve the distress seen during circumcision [16]. In one study by Stang et al, dorsal penile nerve block was found to be effective in reducing behavioral distress and modifying the adrenocortical stress response [20]. It was reported that the injection itself did not increase stress and did not offset the beneficial effects of anaesthesia [19].

The Langerhans cells are an epithelial component of the immune system and lack of the epidermal Langerhans cells at the inner surface of the prepuce may produce reduced immunological response to cutaneous antigens [21]. Perhaps this histological difference between the inner and outer surface of the prepuce may cause reduced cytokine response to sleeve of foreskin and incision.

The macrophages and monocytes start acute phase response at the site of tissue injury by releasing the mediators. Cytokine response to surgery reflects the extent of tissue injury and is decreased with minimally invasive techniques [4]. Wolff et al evaluated the possible tissue damage during extra corporeal shock wave lithotripsy and observed no marked CRP elevations because of minimal tissue damage [22]. In circumcision, the size of injured tissue is small and the systemic absorption of mediators may be decreased because the penis is an end organ.

In conclusion, there was no change in CRP and albumin values as acute phase protein response to circumcision and type of anaesthesia did not affect this response. Although undetectable changes at CRP and albumin concentrations may occur, no stress response to circumcision may be explained with the size of injured tissue or anatomical (end organ) and histological type of the prepuce.

REFERENCES

- [1] Johnson AM, Rohlfs EM, Silverman LM. Proteins. In: Burtis CA, Ashwood ER, eds. *Tietz Textbook of Clinical Chemistry*. 3rd ed. Philadelphia, Pa: WB Saunders; 1999:477–540.
- [2] Moore CM, Desborough JP, Powell H, Burrin JM, Hall GM. Effects of extradural anaesthesia on interleukin-6 and acute phase response to surgery. *Br J Anaesth*. 1994;72(3):272–279.
- [3] Sheeran P, Hall GM. Cytokines in anaesthesia. *Br J Anaesth*. 1997;78(2):201–219.
- [4] Taylor NM, Lacoumenta S, Hall GM. Fentanyl and the interleukin-6 response to surgery. *Anaesthesia*. 1997;52(2):112–115.
- [5] Elder JS. Abnormalities of the genitalia in boys and their surgical management. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, eds. *Campbell's Urology*. 8th ed. Philadelphia, Pa: WB Saunders; 2002:2334–2352.
- [6] Ellis DG, Mann CM. Abnormalities of the urethra, penis and scrotum. In: O'Neill JA, Rowe MI, Grosfeld JL, Fonkalsrud EW, Coran AG, eds. *Pediatric Surgery*. Saint Louis, Mo: Mosby-Year Book; 1998:1783–1795.
- [7] Lerman SE, Liao JC. Neonatal circumcision. *Pediatr Clin North Am*. 2001;48(6):1539–1557.
- [8] Wellington N, Rieder MJ. Attitudes and practices regarding analgesia for newborn circumcision. *Pediatrics*. 1993;92(4):541–543.
- [9] Lander J, Brady-Fryer B, Metcalfe JB, Nazarali S, Muttitt S. Comparison of ring block, dorsal penile nerve block, and topical anesthesia for neonatal circumcision: a randomized controlled trial. *JAMA*. 1997;278(24):2157–2162.
- [10] Johr M, Berger TM. Regional anaesthetic techniques for neonatal surgery: indications and selection of techniques. *Best Pract Res Clin Anaesthesiol*. 2004;18(2):357–375.
- [11] Brix-Christensen V, Tonnesen E, Sorensen IJ, Bilfinger TV, Sanchez RG, Stefano GB. Effects of anaesthesia based on high versus low doses of opioids on the cytokine and acute-phase protein responses in patients undergoing cardiac surgery. *Acta Anaesthesiol Scand*. 1998;42(1):63–70.
- [12] Simpson PJ, Radford SG, Lockyer JA. The influence of anaesthesia on the acute phase protein response to surgery. *Anaesthesia*. 1987;42(7):690–696.
- [13] Booker PD, Taylor C, Saba G. Perioperative changes in α_1 -acid glycoprotein concentrations in infants undergoing major surgery. *Br J Anaesth*. 1996;76(3):365–368.
- [14] Gunel E, Caglayan O, Caglayan F, Sahin TK. Acute-phase changes in children recovering from minor surgery. *Pediatr Surg Int*. 1998;14(3):199–201.
- [15] Khilnani P, Munoz R, Salem M, Gelb C, Todres ID, Chernow B. Hormonal responses to surgical stress in children. *J Pediatr Surg*. 1993;28(1):1–4.
- [16] Jordon GH, Schlossberg SM. Surgery of the penis and urethra. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, eds. *Campbell's Urology*. Philadelphia, Pa: WB Saunders; 2002:3886–3954.
- [17] Buyukkocak U, Caglayan O, Oral H, Basar H, Daphan C. The effects of anesthetic techniques on acute phase response at delivery (anesthesia and acute phase response). *Clin Biochem*. 2003;36(1):67–70.
- [18] Bourguignat A, Ferard G, Jenny JY, Gaudias J. Incomplete or absent acute phase response in some postoperative patients. *Clin Chim Acta*. 1997;264(1):27–35.
- [19] Gregory GA. Pharmacology. In: Gregory GA, ed. *Pediatric Anesthesia*. New York, NY: Churchill Livingstone; 1994:13–45.
- [20] Stang HJ, Gunnar MR, Snellman L, Condon LM, Kestenbaum R. Local anesthesia for neonatal circumcision. Effects on distress and cortisol response. *JAMA*. 1988;259(10):1507–1511.
- [21] Weiss GN, Westbrook KC, Sanders M. The distribution and density of Langerhans cells in the human prepuce: site of a diminished immune response? *Isr J Med Sci*. 1993;29:42–43.
- [22] Wolff JM, Mattelaer P, Boeckmann W, Kraemer U, Jakse G. Evaluation of possible tissue damage in patients undergoing extracorporeal shock wave lithotripsy employing C-reactive protein. *Scand J Urol Nephrol*. 1997;31(1):31–34.