

Effect of prophylactic vitamin D on anesthetic outcome in children with sickle cell disease

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Abstract

Background: Few previous studies proved that complications related to sickle cell disease (SCD) were common with regional anesthesia compared with general anesthesia while others reported no differences. This study was carried out to evaluate the role of prophylactic vitamin D on anesthetic outcome among male children with SCD undergoing circumcision.

Materials and Methods: A comparative study was carried out on 58 children undergoing circumcision with the regional block under light general anesthesia. The study sample was classified into two groups: one group received daily 400 IU vitamin D for 6 months before surgery while the other group without vitamin D. All patients were followed regarding the post-operative analgesia and the incidence of post-operative SCD related complications (acute chest syndrome, painful crisis and cerebrovascular accident). Data were analyzed with Statistical Package for Social Sciences version 13, produced by IBM SPSS, Inc. in Chicago, Illinois, USA.

Results: There was a highly significant difference between the two groups ($P < 0.001$) regarding first analgesic request and total analgesic consumption per day: there was delayed analgesic request and less total analgesic consumption per day in vitamin D group. Comparison of post-operative sedation scores showed highly significant difference ($P < 0.001$) between the two groups, Sedation scores was increased significantly in vitamin D group. This study also reported that the administration of vitamin D was associated with less noticeable post-operative SCD complications.

Conclusion: The use of prophylactic vitamin D in SCD will result in delayed post-operative analgesic request and less total analgesic requirement. Administration of vitamin D was also associated with less post-operative complications.

Key words: Anesthesia, circumcision, sickle cell disease, vitamin D

Introduction

Circumcision is a very common procedure; circumcision in sickle cell disease (SCD) patient is considered as a low risk procedure and could be carried out under general or regional anesthesia.^[1] Regional analgesic techniques are more effective than systemic opioids, non-steroidal anti-inflammatory drugs and acetaminophen for post-operative analgesia in

circumcision.^[2] The most preferred techniques are caudal block and dorsal penile nerve block.^[3] Caudal anesthesia is one of the most frequently used forms of regional anesthetic techniques in children of all ages. Its popularity stems from its simplicity, safety and efficacy in all age groups and is widely used for post-operative pain relief. It may be used as the sole anesthetic in high risk patient and most commonly used in conjunction with general anesthesia. A previous study proved that complications related to SCD including acute chest syndrome, painful crisis and cerebrovascular accident (CVA) were common with the regional anesthesia compared with general anesthesia,^[4] while another study suggested that there were no significant differences.^[5]

SCD is caused by mutations in the β -hemoglobin gene and the affected persons have extremely variable phenotypes. Individuals homozygous for the S gene have sickle cell (SC) anemia while SCD refers to all individuals with either homozygous sickle cell anemia or who are heterozygous for the S and another abnormal beta globin gene.^[6] The

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pathophysiology of this disease is complex and has components of sickle vaso-occlusion and hemolysis.^[7] The bone in SCD is affected by microinfarction, osteopenia, osteoporosis, osteomyelitis and osteonecrosis.^[8] Both low 25-hydroxyl vitamin D [25(OH)D] and low bone mineral density (BMD) have been described in children with SCD.^[9,10] Vitamin D and calcium are required for optimal bone health. 90% of required vitamin D synthesis come from exposure to sunlight. Persons with SCD are at particular risk for vitamin D deficiency (VDD) due to melanin skin hyper-pigmentation, which blocks cutaneous vitamin D production and high rates of lactose intolerance that leads to a reduced intake of vitamin D fortified dairy products. This also might explain, in part, the high incidence of VDD among individuals with SCD who are primarily of African descent.^[11-13]

Studies in Saudi Arabia, the United Arab Emirates, Lebanon, India, Turkey and Australia, revealed that 30-50% of children and adults were deficient in 25(OH)D with levels below 20 ng/ml.^[14] This study was carried out to evaluate the effect of prophylactic vitamin D on post-operative analgesia and post-operative complications among patients with SCD undergoing circumcision.

Materials and Methods

After approval from hospital ethics committee and written informed consent from the parents, 58 male children (aged 2-6 years) belonging to American Society of Anesthesiologists Grade II and scheduled to undergo elective circumcision were enrolled for the study, which was carried out between January and August 2012. A total of 58 patients were included in the study. They were randomly divided into two groups (29 each): Group that was administered 400 IU vitamin D for 6 months (Group 1) and those without vitamin D (Group 2). Blinding was achieved as double-blind (i.e. patients and clinician were unaware with the selection process). Random allocation of the patients belonging to each group was performed by computer-generated random table. Exclusion criteria included severe systemic disease, pre-existing neurological or obvious spinal disease, bleeding diathesis and a history of seizure disorder or a known hypersensitivity to amide-type local anesthetics.

The pre-anesthetic examination comprised of detailed history and systemic examination for end organ damage and acute chest syndrome (ACS). A full neurological examination was performed to elicit any neurological deficit from a previous CVA. Any complications associated with previous blood transfusion, surgery and anesthesia was also assessed. A through airway examination was performed for possible

difficult intubation. Pre-operative investigations included complete blood count, coagulation profile, liver functions, renal functions, chest X-ray and echocardiogram in all patients. All patients followed the standard fasting guidelines prior to surgery.

A 22-gauge intravenous cannula was inserted into the dorsum of the hand in the premedication room. The fluid requirement was calculated depending on the age, weight of the patient and the fasting hours and transfused accordingly. In the operating room, standard monitoring included: pulse oximetry, end tidal carbon dioxide, heart rate, non-invasive blood pressure, electrocardiography and temperature. Dehydration, over hydration, hypoxia, cold exposure and acidosis were avoided.

General anesthesia was induced using sevoflurane with 100% oxygen through Jackson Rees modification of Ayres T piece. Once adequate depth of anesthesia was achieved, laryngeal mask airway (LMA) was inserted and anesthesia was maintained with sevoflurane caudal block was performed in the lateral decubitus position with both knees drawn up. Injecting 0.75 ml/kg bupivacaine (0.25%) subsequently, the surgical procedure was conducted. At the end of circumcision, LMA was removed and the patient was shifted later on to post-anesthesia care unit once they regained protective airway reflexes and regained consciousness. The duration of surgery, duration of anesthesia and first time to rescue analgesia were recorded.

Post-operative analgesia was recorded for the first post-operative day using face, legs, activity, cry, consolability (FLACC) pain evaluation scale [Table 1]. A total score per patient is between 0 and 10. Scores can be grouped as: 0 = relaxed and comfortable; 1-3 = mild discomfort; 4-6 = moderate pain; 7-10 = severe pain. If the FLACC pain^[15] score was ≥ 5 , paracetamol (Perfalgan[®]) was given in a dose of 15 mg/kg, every 4-6 h as slow IV infusion over 15 min for pain relief. Adequate analgesia is necessary for effective physiotherapy, rapid ambulation and rapid discharge from the hospital.

Table 1: FLACC pain evaluation scale

Categories	0	1	2
Face expression	No special expression	Slight frowning, grimace	Mop, teeth clenching
Legs	Normal position	Tight, stressful	Kick at anybody
Activity	Calm	Turn around	Hop off, jerk
Cry	No cry	Groan, moaning	Shouting cry, with screams
Consolability	Relaxed	Consoled with hug or touch	Never consoled

FLACC=Face, leg, activity, cry, consolability

Ramsey Sedation Scale was used for post-operative sedation follow-up:^[16]

- Fully awake and oriented
- Awake, sleepy
- Asleep, but easily awoken by verbal command
- Asleep, but easily awoken by motor stimulation
- Asleep and cannot be awoken by verbal or motor stimulation.

Post-operative complications were evaluated for 24 h after surgery these included:

1. SCD-related complications: ACS, CVA and painful crisis. Painful crisis was defined as pain in the extremities, back, abdomen, chest or head for which no other explanation (e.g., osteomyelitis or appendicitis) could be found. ACS was defined as the new appearance of an infiltrate on chest radiograph or abnormalities on a radioisotope lung scan in the presence of symptoms.
2. Non-SCD-related complications: Fever, infection (excluding ACS), bleeding, thrombosis, embolism and death.
3. Other complications: Transfusion reactions and unspecified complications.

Statistical analysis

Data were analyzed with Statistical Package for Social Sciences version 13, produced by IBM SPSS, Inc. in Chicago, Illinois, USA.

Quantitative variables were tested for normality distribution by the Kolmogorov-Smirnov test. Quantitative variables were presented as mean \pm standard deviation (SD). Qualitative variables were presented as numbers and percentages. The differences between mean \pm SD of the two groups were assessed using an independent *t*-test. Chi square and Fisher's exact test was used to compare the qualitative data. $P \leq 0.05$ was considered to be statistically significant.

Results

The two groups were comparable regarding age, weight, SC genotype and hemoglobin level, duration of anesthesia

and duration of surgery. There was a highly significant difference between the two groups ($P < 0.001$) regarding 25(OH)D level, first analgesic request and total analgesic consumption per day. There were delayed analgesic request and less total analgesic consumption per day in vitamin D group. Sedation scores were significantly high in vitamin D group [Table 2].

Their heart rate was significantly higher in Group 2 throughout the intraoperative period. However, the mean blood pressure was comparable between the two groups [Table 3]. There was no significant difference in oxygen saturation (97.3 ± 2.1 for Group 1 vs. 96.7 ± 1.9 for Group 2) and end tidal carbon dioxide (39.5 ± 3.4 for Group 1 vs. 38.8 ± 3.0 for Group 2) between the two groups.

Table 2: Demographic, laboratory, operative, analgesic and sedation data (mean \pm SD)

Characteristics	Group 1 (n=29)	Group 2 (n=29)	P value
Age (years)	4.6 \pm 1.4	5.0 \pm 1.7	0.332
Weight (kg)	21.7 \pm 4.8	19.5 \pm 4.3	0.071
Sickle cell genotype			
SS	20	22	0.557
SB+thal	6	5	0.738
SC	3	2	1
Hemoglobin (g/dl)	8.12 \pm 1.1	7.93 \pm 0.9	0.475
25-hydroxyl vitamin D (ng/ml)	32.5 \pm 8.3	15.7 \pm 4.2	<0.001**
Duration of anesthesia (min)	27.3 \pm 6.2	26.5 \pm 7	0.646
Duration of surgery (min)	16.8 \pm 6.2	18.7 \pm 4.5	0.187
The first analgesic request (min)	414 \pm 32	321 \pm 20	<0.001**
Total paracetamol (mg/day)	945 \pm 120	1123 \pm 156	<0.001**
Ramsey sedation score			
After 6 h	2.84 \pm 0.75	2.13 \pm .87	<0.001**
After 24 h	2.98 \pm 0.67	2.34 \pm 0.46	<0.001**

Group 1 with vitamin D, Group 2 without vitamin D. SS=Sickle cell anemia, SC=Sickle-hemoglobin C disease, SB+thal=Sickle- β -thalassemia, SD=Standard deviation. **Highly significant when $P \leq 0.001$

Table 3: Hemodynamic changes among the studied groups

Time	Mean blood pressure			Heart rate		
	Group 1	Group 2	P value	Group 1	Group 2	P value
Pre-operative	66.5 \pm 5.8	65.9 \pm 6.2	0.7050	112.1 \pm 9.6	115 \pm 10.3	0.272
5 min intraoperative	68.3 \pm 6.8	69.5 \pm 7.2	0.5167	115.3 \pm 10.2	127.2 \pm 12.2	<0.001**
10 min intraoperative	63.4 \pm 4.8	62.1 \pm 5.2	0.3268	114.9 \pm 8.2	120.1 \pm 10.4	0.035*
15 min intraoperative	65.9 \pm 5.5	67.1 \pm 4.8	0.3798	103 \pm 8.4	118 \pm 7.5	<0.001**
20 min intraoperative	63.8 \pm 4.4	66.0 \pm 6.2	0.1248	101 \pm 10.1	108 \pm 8.8	0.005**
25 min intraoperative	64.7 \pm 4.2	67.16 \pm 6.9	0.1152	100 \pm 9.7	106 \pm 8.6	0.01**

Group 1 with vitamin D, Group 2 without vitamin D. *Significant when $P \leq 0.05$, **Highly significant when $P \leq 0.01$

Circumcision is a minor procedure and all our patients did not receive any intraoperative or post-operative blood transfusions. Although the differences between the two groups regarding SCD-related post-operative complications were insignificant ($P = 0.371$), there was a noticeable difference between the two groups regarding the incidence of SCD related complications. Painful crisis was the most commonly observed SCD-related post-operative complication wherein, the risk among the non-vitamin D group was 4 folds more than the vitamin D group (3.4% in vitamin D group vs. 13.7% in the other group). Fever as a non-SCD-related post-operative complication was occurred only among the second group (6.8%). Retention of urine was recorded in both groups.

Discussion

Circumcision is the most common surgical procedure in children.^[17] It is widely accepted that pain control should be provided after circumcision for ethical, humanitarian and physiological reasons.^[17,18]

Our study revealed a significant decrease in post-operative demand for analgesics in vitamin D group while urine retention was the most prominent reported complication of caudal block among both groups.

Hemoglobin S produces a problem of erythrocyte sticking; instead of simply erythrocyte was sickling. Adhesion, hemolysis and deformation are interlinked, together leading to profound disruption of the vascular function.^[7] Deficiencies of calcium and vitamin D in utero and in childhood may prevent the maximum deposition of calcium in the skeleton.^[19] While treatment with vitamin D and calcium improved both 25(OH)D levels and BMD, long-term vitamin D and calcium therapy is likely to be required given the chronicity of SCD and its relentless vaso-occlusive hemolytic and inflammatory complications. Because low BMD was observed in young adults, screening for VDD should be considered at an earlier age, preferably in childhood.^[9] It was reported that VDD has been linked to chronic pain including pain with SCD, arthralgia, leg pain in older adults, headache, postherpetic neuralgia, diffuse bone and muscle pain and chronic back pain.^[20] Furthermore, Colleen suggested that not only an association of low vitamin D levels with various pain syndromes, but also an improvement in symptoms with vitamin D repletion.^[21] Furthermore, supplementation of vitamin D may serve a dual role in SCD patients by helping to improve both bone health and the chronic pain experience. The treatment of VDD led to improvement in pain symptoms and decreased the use of pain medications in non-SC subjects with the chronic pain.^[22,23]

Osunkwo *et al.* reported that with advance of age, individuals with SCD experience daily chronic pain. He gave a 6-week course of oral high-dose vitamin D (4000-100 000 IU/week) for children and adolescents SCD subjects with vitamin D insufficiency and deficiency and monitored prospectively for a period of 6 months. Subjects who received this high-dose of vitamin D achieved higher serum 25(OH)D, experienced fewer pain days per week and had higher physical activity quality-of-life scores. These findings suggest a potential benefit of vitamin D in reducing pain in SCD.^[20,24] Vieth reported that excessive amounts of Vitamin D can be harmful to infants and may be characterized by nausea and vomiting, loss of appetite, excessive thirst, frequent urination, constipation, abdominal pain, muscle weakness, muscle and joint aches, confusion, fatigue and may be kidney damage. Vitamin D intoxication is extremely rare, but can be caused by inadvertent or intentional ingestion of excessively high doses. Doses of 10,000 IU of vitamin D3 per day for up to 5 months, however, do not cause toxicity.^[25] In our work, we started prophylactic vitamin D before surgery for the same period of time and it was associated with a significant decrease analgesic requirements and at the same time the post-operative complications were noticeably less among these patients (both related and non-related to SCD). Vitamin D group was associated with significant intraoperative slow heart rate and also highly significant higher sedation scores, which may be contributed to the effect of vitamin D in SCD patients.

The most important limitations of this study were that the post-operative follow-up was only for 24 h, the number of patients in each group was small and the short course of prophylactic vitamin D used. Furthermore, we suggest a study to evaluate gender difference.

The results of the present study reveal that the use of prophylactic vitamin D in SCD resulted in delayed post-operative analgesic request and less total analgesic consumption. Administration of vitamin D was also associated with noticeable less post-operative SCD complications. This work focused on the significance of vitamin D in management of SCD patients. Prophylactic vitamin D has proved a modifiable effect on the anesthetic outcome in male SC children subjected to circumcision.

Further studies are indicated which involve both genders; different nations and use of vitamin D for long duration in patients with SCD need to determine the overall efficacy of this therapy.

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