Hemodynamic Responses to Captopril During Splenectomy in Thalassemic Children

VORAPA SUWANCHINDA, M.D.*,
SANGSOM PIRAYAVARAPORN, M.D.*,
MONGKOL LAOHAPENSANG, M.D.***
VORAVARN TANPHAICHITR, M.D., M.S.**,
PRADIT SOMPRAKIT, M.D.*,

Abstract

Splenectomy in ß-thalassemic children is frequently accompanied by perioperative hypertension which occasionally is followed by convulsion. The efficacy of captopril in attenuating the hypertensive response to splenectomy was investigated in 82 thalassemic children. The control group, consisting of 40 patients, received intravenous furosemide (1 mg/kg) preoperatively; whereas, 42 children were randomly allocated into 2 groups to receive oral captopril (0.7 mg/kg) or a combination of captopril (0.7 mg/kg) and furosemide (1 mg/kg) before the operation.

Before anesthetic induction, both systolic and diastolic arterial pressures in the captopril and the combined groups were significantly lower than the furosemide group ($P<0.001$), whereas, the heart rates in all groups were comparable. Changes in arterial pressure in response to the operation were significantly smaller in the combined group when compared with the other two groups ($P<0.001$). Immediate postoperative hypertension requiring additional management occurred in 20 per cent of the furosemide group, and 14.3 per cent in the other two groups. One patient in the combined group had a convulsion in association with hypertension. The authors conclude that captopril combined with furosemide effectively controls intraoperative hypertension in thalassemic children undergoing splenectomy; however, postoperative hypertension remains common, and needs appropriate treatment immediately.

Key word : Thalassemia, Splenectomy, Hypertension, Captopril

* Department of Anesthesiology,
** Department of Pediatrics,
*** Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

The thalassemia syndromes are the most common disorders of hemoglobin synthesis, that are concentrated in the population of the Mediterranean, Middle East and Southeast Asia, including Thailand. The thalassemia major patients usually require regular blood transfusion to prevent the adverse effects of chronic anemia on growth, development and organ functions. Removal of the spleen in severe ß-thalassemic patients is often necessary when the annual blood requirement is massively increased from hypersplenism[1-3]. Surgical risks in experienced hands are minimal eventhough the spleens are extremely enlarged. Several anesthetic hazards have been described in these patients, resulting from multiple organ involvement; such as difficulty in airway management related to facial bone deformities, congestive heart failure associated with intravascular volume overload, cardiomyopathy and organ dysfunction caused by hemosiderosis[4-7]. Besides, hemodynamics augmentation have been recognized and require closer observation because perioperative hypertension related to splenectomy may proceed to an unfavorable result of hypertensive encephalopathy[8]. Expansion of blood volume from autotransfusion during surgical manipulation of the spleen has been speculated; however, reduction of excessive circulatory volume by administering furosemide does not effectively prevent adverse cardiovascular events[9]. Since it has been reported that ß-thalassemia/hemoglobin E patients have a high basal plasma renin activity (PRA) level[10], renin angiotensin system activation may cause hypertension under this circumstance. Therefore, angiotensin converting enzyme inhibitors may be useful in controlling blood pressure during the perioperative period in these patients.

The current study was conducted to compare the efficacy of captopril, the angiotensin converting enzyme inhibitor, with furosemide for reducing hypertensive responses in thalassemic children undergoing splenectomy.

MATERIAL AND METHOD

Eighty-two consecutive ß-thalassemic children, ASA II-III, scheduled for elective splenectomy or combined splenectomy and cholecystectomy at Siriraj Hospital, Mahidol University, were included in this study. Their parents gave informed consent for the study, which was approved by the Institutional Ethics Committee. Forty patients in the control group were assigned to receive intravenous furosemide before anesthetic induction. In 82 patients, 42 were randomly assigned to receive captopril, or captopril combined with furosemide.

Each patient in all groups received an oral premedication with 0.2 mg/kg of diazepam approximately 1-2 h before anesthetic induction. In captopril treated groups, a single oral dose 0.7 mg/kg of this drug was given following the premedication. The preparation was obtained by dissolving a 25 mg tablet of captopril in water, the appropriate aliquots of resulting solution with 30 ml of diluted colorful syrup were then administered to the patients under the supervision of a staff anesthesiologist.

Before inducing anesthesia, pulse oximetry and electrocardiographic monitoring were continuously recorded. Measurement of arterial pressure was obtained by using the automatic noninvasive monitor (Colin Model 1001S), recorded systolic, mean and diastolic pressures every 2 min during anesthetic induction and tracheal intubation, then every 5 min throughout the operation.

With the exception of the group in which only captopril was given, intravenous furosemide 1 mg/kg was given immediately before anesthetic induction. General anesthesia was induced in all groups with thiopental 3-5 mg/kg, followed by succinylcholine 1-2 mg/kg and fentanyl 1-2 µg/kg. Trachea was intubated for mechanically controlled ventilation. Anesthesia was maintained with approximately 50 per cent nitrous oxide and 0.5-1 per cent halothane in oxygen. Atracurium 0.5 mg/kg was given to achieve adequate muscle relaxation. Urinary bladder was catheterized before performing the operation. As soon as the operation was completed, antagonism of neuromuscular blockade was achieved by giving atropine and neostigmine.

During the postoperative period, the heart rate as well as arterial pressure was recorded, initially by recovery room nurses, and subsequently by ward nurses who were blind from the type of intervention. Abnormal neurological findings such as convulsion, abnormal movement or disorientation were also observed. Pethidine 1-2 mg/kg was administered intramuscularly in 6 h period for providing adequate pain relief. A physician should be notified and appropriate treatment given if the arterial pressure increased higher than 130/90 mmHg, or when any abnormal neurological symptoms had developed.

Table 1. Demographic data.

	Furosemide	Captopril	Combined
Sample size (n)	40	21	21
Age (yr)	7.05 ± 3.41	8.19 ± 3.16	7.98 ± 2.76
Weight (kg)	17.57 ± 5.62	17.93 ± 5.01	17.86 ± 4.66
Hematocrit (%)	26.43 ± 3.94	24.90 ± 3.18	25.28 ± 3.16
Anesthetic time (min)	86.12 ± 26.85	78.42 ± 14.14	93.10 ± 27.95

Data are presented as mean ± SD.
No significant difference exists among groups; P <0.05 considered significant.

Analysis of variance was used for comparison of patients' characteristic data. The incidence of postoperative hypertension and the need for antihypertensive agents were compared by using the chi square test. A repeated measured analysis of variance was performed for comparison of heart rate, systolic and diastolic arterial pressures. If there were any differences among the groups, the data would be compared by using one way analysis of variance, and followed by modified least significant difference test. Paired *t* test was used for analysis of paired samples between the different times in each group. P <0.05 was considered statistically significant.

RESULTS

The three groups were comparable in age, weight, preoperative hematocrit and duration of anesthesia (Table 1).

Before inducing anesthesia, the heart rate in all groups was comparable, whereas, the systolic and diastolic arterial pressures in the captopril and the combined groups were significantly lower than the furosemide group (P<0.001). However, none of the patients in all groups had excessive hypotension (defined as a systolic pressure less than or equal to 70 mmHg). Tracheal intubation and surgery caused significant hemodynamic augmentation in all patients. The increases in heart rate were comparable among the groups, each group exhibited the greatest response to tracheal intubation (P<0.01), which was followed by reducing towards basal value in the postanesthetic period (Fig. 1). All three groups showed maximum increase in systolic and diastolic pressures during tracheal intubation (P<0.001). These changes also declined towards the control values on termination of anesthesia (Fig. 2), but were significantly lower in the combined group compared with the furosemide and the captopril groups (P <0.001).

Bradycardia with the heart rate decreased to less than 60 beats/min occurred in two patients

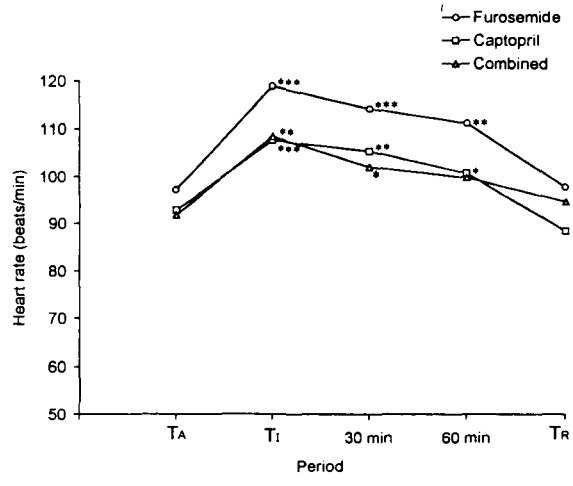

Fig. 1. Changes in heart rate measured immediately before anesthetic induction (TA), during tracheal intubation (TI), at 30 min and 60 min after induction, and 30 min after surgery (TR). Tracheal intubation and surgery caused significant increases in heart rate in all groups, which were followed by decreasing towards basal values in the recovery period. However, heart rate changes among groups were not statistically different.
*** P <0.05, ** P<0.01, *** P<0.001 compared to the respective value measured immediately before anesthetic induction.**

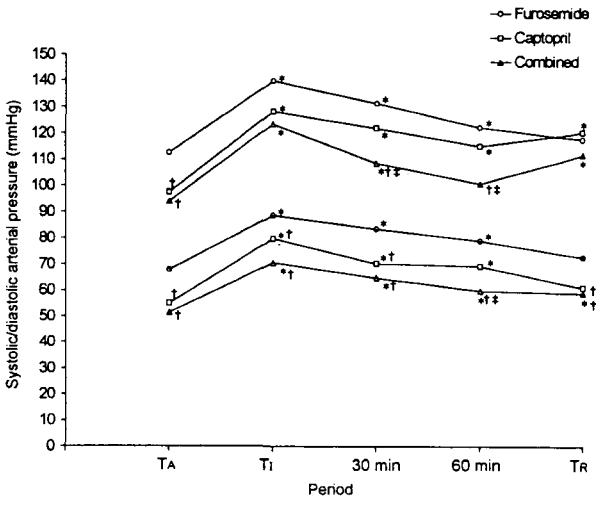

Fig. 2. Changes in systolic and diastolic arterial pressures measured immediately before anesthetic induction (TA), during tracheal intubation (TI), at 30 min and 60 min after induction, and 30 min after surgery (TR). Before anesthetic induction, the systolic and diastolic arterial pressures in the captopril and the combined groups were significantly lower than the furosemide group. All three groups showed maximum increase in systolic and diastolic pressure during tracheal intubation. Changes in arterial pressure in response to the operation were significantly less in the combined group when compared to the captopril and the furosemide groups. * P<0.01 compared to the respective value measured immediately before anesthetic induction.
† P<0.05 compared to furosemide.
‡ P<0.001, combined compared to captopril.

during the study, one belonged to the captopril group and the other was in the combined group; both showed satisfactory response to a bolus of 0.2 mg of atropine given intravenously. One patient in the combined group vomited a liquid content, containing a colorful syrup; however, none of the patients developed serious pulmonary aspiration in this study.

In the first 24 h postoperation, the incidence of hypertension (defined as the arterial pressure increased to more than 130/90 mmHg) in the furosemide, the captopril and the combined groups were 20 per cent, 14.3 per cent and 14.3 per cent respectively. These hypertensive patients were treated with 1 mg/kg furosemide intravenously. However, 10 per cent and 9.5 per cent of patients in the furosemide and combined groups required additional treatment with reserpine, hydralazine or sublingual nifedipine to normalize the arterial pressure, while no patient in the captopril group required such treatment. One patient in the combined group previously had normal blood pressure during the study, suffered from late hypertension on the second day, and further developed convulsion followed by a stroke.

DISCUSSION

In the present study, a single oral dose of captopril 0.7 mg/kg given 1-2 h before anesthetic induction produced a significant decrease in basal level of systolic and diastolic arterial pressures in our thalassemic patients, compared to furosemide. Hypotensive responses after a single dose of captopril as described by Daman Willems et al[11] were significantly correlated with initial PRA. A dose 0.7 mg/kg was suggested in their study to provide a safe and effective screening test for identifying hypertensive children with raised PRA. Thalassemic patients are known to have a higher level of PRA than normal children[10], furthermore their blood volumes also increase consequently from severe chronic anemia. This may explain absence of excessive hypotension in those who received captopril in this study. In addition, our data demonstrated that captopril combined with furosemide significantly minimized pressure responses to surgical stimuli in thalassemic patients. We found in common with another author that this drug reduced arterial pressure without producing reflex tachycardia[12]. We actually found intraoperative bradycardia in two patients after captopril. Removal of an excessively enlarged spleen can stimulate vagal reflex; as angiotensin II facilitate the sympathetic effect[13], so the blockade of its activity may result in enhancement of this reflex. These two cases responded promptly to the parasympatholytic effect of atropine.

Vomiting during anesthetic induction was found in one patient to whom captopril was given before the operation. This could be related to the amount of ingested fluid containing preoperative oral medication. Mirkin et al[14] recommended

crushing a 25 mg captopril tablet, added to 25 ml of water and shaken well for at least 5 min if doses of less than 12.5 mg were required. The mixture was restricted to 30-60 ml after adding a diluted colorful syrup; however, this content still persisted in the stomach until the time of anesthetic induction. We assumed that massive hepatosplenomegaly which was common in our thalassemic children could considerably prolong gastric emptying.

The incidence of postoperative hypertension in the immediate 24 h was not only significantly different among groups, but also quite similar to our previous studies[8,9]. A single dose of captopril was found insufficient for controlling postoperative hypertension, because its antihypertensive action disappears by 4-8 h[15]. In this study, furosemide, a combined reserpine and furosemide, with the addition of hydralazine or sublingual nifedipine were chosen for reducing postoperative hypertension, because these had been used successfully in our thalassemic patients who suffered from posttransfusion hypertension[16]. Most of the patients in all groups effectively responded to this therapy. However, one patient with a delayed onset of hyperten sion eventually developed convulsion and followed by right hemifacial palsy. Infarction of the right frontal cortex including parietal lobes was diagnosed by computerized tomography of the head. Cerebral thrombosis induced by hypertension was suspected to be the major cause of stroke in this patient. Leeman et al[17] reported that sublingual captopril and nifedipine were equally effective for the treatment of arterial hypertension after abdominal aortic surgery. As shown in this study, combined captopril with furosemide effectively reduced the arterial pressure during splenectomy in thalassemic children, therefore, a repeated dose of this drug may be employed sublingually for treatment as well as prevention of postoperative hypertension when the oral medication is unsuitable.

We conclude that in thalassemic children undergoing splenectomy, combined captopril and furosemide proved to be more effective in controlling intraoperative hypertension than captopril or furosemide alone. Postoperative hypertension is still a common manifestation among these patients, therefore treatment with antihypertensive drugs remains necessary.

(Received for publication on September 8, 1997)

REFERENCES

1. Modell B. Total management of thalassemia major. Arch Dis Child 1977; 52: 489-500.
2. Glaziano JH, Piomelli S, Hilgartner M, et al. Chelation therapy in beta-thalassemia major : III. The role of splenectomy in achieving iron balance. J Pediatr 1981; 99: 695-9.
3. Cohen A, Markeson AL, Schwartz E. Transfusion requirements and splenectomy in thalassemia major. J Pediatr 1980; 97: 100-2.
4. Orr D. Difficult intubation: A hazard in thalassemia. A case report. Br J Anaesth 1967; 39: 585-6.
5. Jootar P, Fucharoen S. Cardiac involvement in beta-thalassemia hemoglobin E disease: Clinical and hemodynamic findings. Southeast Asian J Trop Med Publ Health 1990; 21: 269-73.
6. Sonakul D, Thakengpol K, Pacharee P. Cardiac pathology in 76 thalassemic patients. Birth Defects 1988; 23: 177-91.
7. Masera G, Jean G, Conter V, Terzoli S, Mauri RA, Cazzaniga M. Sequential study of liver biopsy in thalassemia. Arch Dis Child 1980; 55: 800-2.
8. Suwanchinda V, Tengapirak Y, Udomphunthurak S. Hypertension perioperative splenectomy in thalassemic children. J Med Assoc Thai 1994; 77: 66-70.
9. Suwanchinda V, Pirayavaraporn S, Yokubol B, Tengapirak Y, Laohapensang M, Udomphunthurak S. Does furosemide prevent hypertension during perioperative splenectomy in thalassemic children? J Med Assoc Thai 1995; 78: 542-6.
10. Snongchart N, Thirawarapan S, Fucharoen S, Tanphaichitr VS. Plasma renin activity in patients with ?? thalassemia hemoglobin E. Birth Defects 1988; 23: 257-62.
11. Daman Willems CE, Shah V, Uchiyama M, Dillon MJ. The captopril test: an aid to investigation of hypertension. Arch Dis Child 1989; 64: 229-34.
12. Morsi MR, Madina EH, Anglo AA, Soliman AT. Evaluation of captopril versus reserpine and frusemide in treating hypertensive children with acute post-streptococcal glomerulonephritis. Acta Paediatr 1992; 81: 145-9.
13. Vinci JM, Howitz D, Zusman RM, Pisano JJ, Catt KJ, Keiser HR. The effect of converting enzyme inhibition with SQ 20,881 on plasma and urinary

kinins, prostaglandin E and angiotensin II in hypertensive man. Hypertension 1979; 1: 416-26.
14. Mirkin BL, Newman TJ. Efficacy and safety of captopril in treatment of severe childhood hypertension: report of the international collaborative study group. Pediatrics 1985; 75: 1091-100.
15. Parrillo JE. Vasodilator therapy. In: Chernow B, ed. Williams and Wilkins, Baltimore, 1989: 406-24.
16. Tanphaichitr VS, Suvatte V, Mahasandana C, Tuchinda S. Hypertension post-transfusion in Thai thalassemic children: Early detection and management. Birth Defects 1989; 23: 251-5.
17. Leeman M, Degaute JP. Invasive hemodynamic evaluation of sublingual captopril and nifedipine in patients with arterial hypertension after abdominal aortic surgery. Crit Care Med 1995; 23: 843-7.

ผลของยาแคพโตพริลต่อการไหลเวียนเลือดระหว่างการตัดม้ามในผู้ป่วยธาลัสซีเมีย

วรภา สุวรรณจินดา, พ.บ., วรวรรณ ตันไพจิตร, พ.บ. M.S.**, แสงโสม ปิรยะวราภรณ์, พ.บ.*, ประดิษฐ์ สมประกิจ, พ.บ.*, มงคล เลาหเพ็ญแสง, พ.บ.****

การตัดม้ามในเด็กโรคเบต้าธาลัสซีเมียนั้นอาจมีอันตรายจากภาวะความดันโลหิตสูงเพราะมีโอกาสทำให้เกิดภาวะแทรกซ้อนทางระบบประสาทตามมาได้ ผู้วิจัยได้ทำการศึกษาฤทธิ์ของยาแคพโตพริล สำหรับลดความดันเลือดในผู้ป่วยกลุ่มนี้จำนวน 82 ราย โดย 40 รายแรกเป็นกลุ่มควบคุมจะได้รับยาฟูโรเซไมด์ 1 มก./กก.บริหารทางหลอดเลือดดำก่อนเริ่มผ่าตัด ผู้ป่วยอีก 42 รายนั้นแบ่งเป็นสองกลุ่มด้วยวิธีสุ่ม โดยจะให้รับประทานยาแคพโตพริล 0.7 มก./กก.ก่อนเริ่มนำสลบ 1–2 ชั่วโมง หรือให้รับประทานยาแคพโตพริล 0.7 มก. /กก.ร่วมกับบริหารยาฟูโรเซไมด์ 1 มก./กก.ทางหลอดเลือดดำ จากผลการศึกษาพบว่ายาแคพโตพริล และแคพโตพริลร่วมกับฟูโรเซไมด์ ลดความดันเลือดทั้ง systolic และ diastolic ในระยะก่อนนำสลบต่ำกว่าเมื่อได้รับยาฟูโรเซไมด์ชนิดเดียว ($P < 0.001$) ขณะที่อัตราเร็วของหัวใจเต้นในผู้ป่วยทั้งสามกลุ่มนั้นไม่แตกต่างกัน แม้ว่าการผ่าตัดกระตุ้นให้ความดันเลือดสูงขึ้นในผู้ป่วยทุกราย ($P < 0.01$) แต่การเปลี่ยนแปลงนี้จะน้อยกว่าในกลุ่มที่ได้รับยาแคพโตพริลร่วมกับฟูโรเซไมด์ ($P < 0.001$) อย่างไรก็ดีระยะ 24 ชั่วโมงแรกหลังผ่าตัดพบภาวะความดันโลหิตสูงมากกว่า 130/90 มม.ปรอท ร้อยละ 20 ในกลุ่มที่ได้รับ ฟูโรเซไมด์ และร้อยละ 14.3 ในผู้ป่วยอีกสองกลุ่ม คณะผู้วิจัยสรุปว่ายาแคพโตพริลร่วมกับฟูโรเซไมด์ลดความดันเลือดได้ดีระหว่างการตัดม้ามในผู้ป่วยธาลัสซีเมีย แต่เนื่องจากยานี้มีฤทธิ์สั้นความดันเลือดจึงสูงขึ้นในระยะหลังผ่าตัด ดังนั้นต้องติดตามดูแลผู้ป่วยเพื่อให้การรักษาที่เหมาะสมต่อไป

คำสำคัญ : ธาลัสซีเมีย, ตัดม้าม, ความดันโลหิตสูง, แคพโตพริล

* ภาควิชาวิสัญญีวิทยา,
** ภาควิชากุมารเวชศาสตร์,
*** ภาควิชาศัลยศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพฯ 10700