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Original Article

The effect of dexmedetomidine on S-100 β in beach chair position for arthroscopic shoulder surgery. A randomized controlled trial

Ji-Su Jang[1], Sung-Mi Hwang[1], Jung-Taek Hwang[2], Young-Ki Kim[3], Jun-Young Sohn[3], Jae-Jun Lee[1]

Departments of [1]Anesthesiology and Pain Medicine, [2]Orthopedic Surgery, Chuncheon Sacred Heart Hospital, College of Medicine, Hallym University, Chuncheon, Korea; [3]Department of Anesthesiology and Pain Medicine, Gangneung Asan Hospital, College of Medicine, Ulsan University, Gangneung, Korea

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Abstract: Objective: This study was designed to determine whether S-100 β is released during arthroscopic shoulder surgery in the beach chair position (BCP). The primary aim was to evaluate the pattern of S-100 β release after BCP and the secondary aim was to explore the effect of dexmedetomidine (DEX) as an adjuvant of interscalene block on the release of S-100 β. Methods: Fifty patients, undergoing arthroscopic rotator cuff repair in the BCP under general anesthesia, were randomly allocated to two groups. Ultrasound-guided interscalene block was performed using 9 ml of 0.75% ropivacaine with 1 ml of normal saline (Group R) or 100 μg of DEX (Group RD). For the S-100 β assay, venous blood was taken at admission and 1, 6, 24, and 48 hours after surgery. Results: Initial S-100 β levels (pg/ml) were 15.13 ± 14.19 (Group R) and 13.74 ± 9.18 (Group RD). They showed peak elevation at 1 hour after surgery [40.78 ± 21.01 (Group R), 28.19 ± 12.63 (Group RD)] and decreased gradually. There was an overall significant difference in the change in S-100 β over time between the two groups (P = 0.029). Conclusions: The S-100 β level was elevated more than two-fold 1 hour after arthroscopic shoulder surgery in the BCP and decreased gradually during the postoperative period, but remained within the normal range. Perineural DEX suppressed the release of serum S-100 β and may serve as a protective agent against cerebral ischemic changes in high-risk patients undergoing arthroscopic shoulder surgery in the BCP.

Keywords: Arthroscopy, beach chair position, cerebral ischemia, dexmedetomidine, S-100 β, shoulder surgery

Introduction

Arthroscopic repair of the rotator cuff is one of the most common surgical procedures for the shoulder, and approximately two-thirds of patients undergo surgery in the sitting or beach chair position (BCP) [1, 2]. However, rare complications including ischemic brain and spinal cord injury after shoulder surgery in the BCP have recently been reported [3-5].

S-100 β is an early cerebral biochemical marker for brain ischemic damage. Slightly elevated levels may be an early sign of future neuronal damage, triggered or accompanied by blood-brain barrier (BBB) failure [6]. Abnormally elevated serum levels of S-100 β are associated with postoperative cerebral complications after cardiac surgeries [7, 8]. Dexmedetomidine (DEX), a selective agonist of α_2-adrenergic receptors, can be an effective adjuvant to local anesthetics for peripheral nerve block [9]. In addition, DEX was shown to induce a neuroprotective effect by increasing astrocyte expression of brain-derived neurotrophic factor and also promotes ischemic tolerance [10, 11].

The primary aim of this study was to evaluate the release pattern of S-100 β, which is a useful biomarker for cerebral ischemic changes, after arthroscopic shoulder surgery in the BCP. The secondary aim was to explore the effect of perineural DEX as an adjuvant of interscalene block on the release of S-100 β.

Materials and methods

Study design and patient selection

This prospective study received Institutional Review Board approval, and the protocol of this

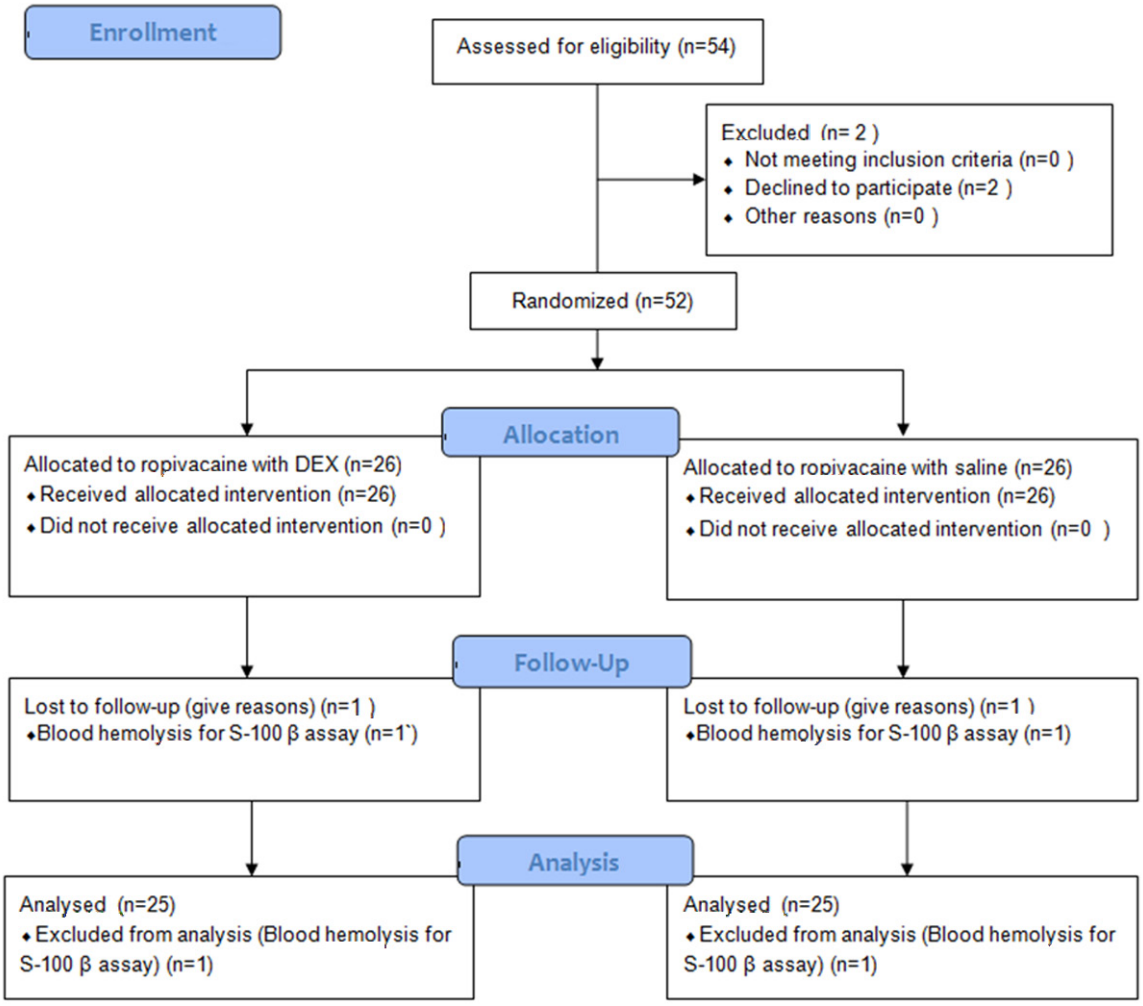

Figure 1. Flow chart of patient enrollment. DEX, dexmedetomidine. Group RD received 9 mL of ropivacaine (0.75%) with 100 μg of dexmedetomidine for interscalene block. Group R received 1 mL of normal saline instead of DEX.

clinical trial was registered on the Clinical Information Service (available at: http://cris.nih.go.kr, KCT0001586). Written informed consent was obtained from the enrolled patients, all of whom were aged >20 years and underwent arthroscopic rotator cuff repair in the BCP. Patients having any contraindication to interscalene block, a history of cerebrovascular accident, dementia, psychiatric disease, or renal disease were excluded.

Double-blinded randomization was performed as follows. Randomization was performed with a computerized random-sequence generator by an independent nurse who prepared a syringe for combined DEX, according to the assignment. The patients and all medical staff members who participated in the operation were blinded to the assignment.

Fifty-four patients who were scheduled for arthroscopic rotator cuff repair in the BCP were assigned to one of two groups. Before the surgery, two patients declined to participate and were excluded. The remaining 52 patients were randomly assigned to one of two groups depending on the use of DEX for the interscalene block. After the surgery, two patients were excluded due to hemolysis of the blood sample for the S-100 β assay. Finally, 50 patients were included in this study. Twenty-five patients were assigned to Group R, and the other 25 patients were assigned to Group RD (**Figure 1**).

Anesthesia and interscalene block

After arrival in the operating room, standard monitoring was performed using electrocardiography, pulse oximetry, noninvasive blood pre-

Table 1. Demographic data

	Group R (n = 25)	Group RD (n = 25)
Age (years)	61.2 ± 8.2	58.1 ± 7.6
Sex (M/F)	16/9	19/6
Height (cm)	160.1 ± 6.9	164.3 ± 9.1
Weight (kg)	67.6 ± 7.9	68.3 ± 13.1
BMI (kg/m^2)	26.9 ± 3.1	25.1 ± 3.2
Duration of BCP (min)	103.2 ± 20.4	100.8 ± 20.7
Duration of operation (min)	79.2 ± 16.6	77 ± 20.6
Duration of anesthesia (min)	129.2 ± 17.7	128 ± 21.6

Values are expressed as mean ± SD or number of patients. Group RD received 9 mL of ropivacaine (0.75%) with 100 μg of dexmedetomidine for the interscalene block. Group R received 1 mL of normal saline instead of dexmedetomidine. BCP, beach chair position. BMI, body mass index.

ssure at the non-operative upper extremity, and bispectral index (BIS). Anesthesia was induced with propofol (2 mg/kg) and rocuronium (0.8 mg/kg). After endotracheal intubation, ventilation was mechanically controlled by 50% oxygen in an air mixture to maintain the end tidal carbon dioxide tension ($EtCO_2$) at 35 to 40 mmHg. The BIS was maintained at 40-60. Anesthesia was maintained with sevoflurane and remifentanil. For invasive blood pressure monitoring, a radial arterial catheter was inserted in the non-operative arm. The pressure transducer of the radial artery pressure measurement was zeroed at the level of the external auditory meatus throughout the surgery. Once monitoring was established, patients were randomly allocated to Group R and Group RD. Ultrasound-guided interscalene block using 0.75% ropivacaine 9 ml with normal saline 1 ml (Group R) or ropivacaine 9 ml with DEX 100 μg (Group RD) was performed on the side of the operative upper extremity by one anesthesiologist.

Beach chair position and hemodynamic management

The patient was then positioned in an approximately 80° head-up position (BCP) using the shoulder accessory for Amsco 3085 SP (Amsco® 3085 Surgical Table; Steris Co., Mentor, OH, USA). After positioning, the head of the patient was secured in a neutral position to ensure that venous drainage was not impaired. Hypotension was defined as a decrease in systolic blood pressure by more than 20% of the preanesthetic value or below 90 mmHg. Bradycardia was defined as a decrease in heart rate (HR) to below 50 beats per minute. Hypotension was treated with phenylephrine, ephedrine, and intravenous fluid loading (4 ml/kg). Bradycardia was treated by intravenous atropine 0.5 mg. All surgical procedures were performed by one surgical specialist in arthroscopic shoulder surgery. After surgery, the patients were repositioned in the supine position. Anesthesia was discontinued and the neuromuscular block was reversed. After obtaining adequate awakening, the patients were extubated and transported to the recovery room.

S-100 β measurement

For S-100 β assay, blood was taken from the peripheral vein after admission and at 1, 6, 24, and 48 hours after surgery. Venous blood was centrifuged at 3,000 rpm for 10 min and serum was frozen within 30 minutes at -70°C until the time of assay at the end of the study. Serum S-100 β was measured using a commercially available ELISA kit (Human S100B ELISA, EZ-HS100 β-33K, Merck Millipore Corp., Billerica, MA, USA). The limit of sensitivity of the assay is 2.7 pg/ml.

Statistical analysis

The sample size was calculated using power analysis (with $\alpha = 0.05$ and power = 0.8) depending on our preliminary study results (mean difference = 13.15, SD = 15.9, effect size = 0.83). A total of 24 patients were required in each group. Data are expressed as numbers or means ± standard deviation. All analyses were performed using SPSS for Windows software (ver. 15.0; SPSS Inc., Chicago, IL, USA). An independent t-test was used for comparison of HR, mean arterial pressure (MAP), and S-100 β at each time point between the two groups. The S-100 β level in serum over time was analyzed based on repeated-measures analysis of variance. A comparison regarding the use of vasopressors was performed with chi-square and independent t-tests. *P*-values less than 0.05 were accepted as indicative of statistical significance.

Results

Fifty patients undergoing arthroscopic rotator cuff repair in the BCP under general anesthesia

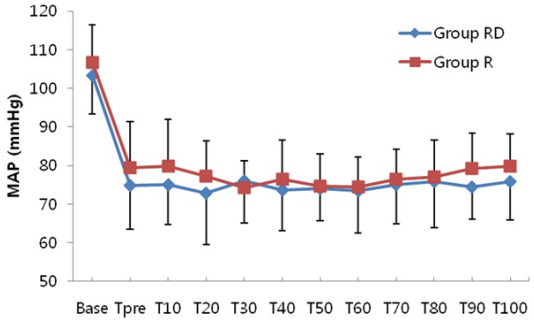

Figure 2. Changes in mean arterial pressure in the beach chair position. Base, at preanesthesia; Tpre, before BCP; T_{10}-T_{100}, at 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 min after beach chair position. Group RD received 9 mL of ropivacaine (0.75%) with 100 μg of dexmedetomidine for interscalene block. Group R received 1 mL of normal saline instead of dexmedetomidine.

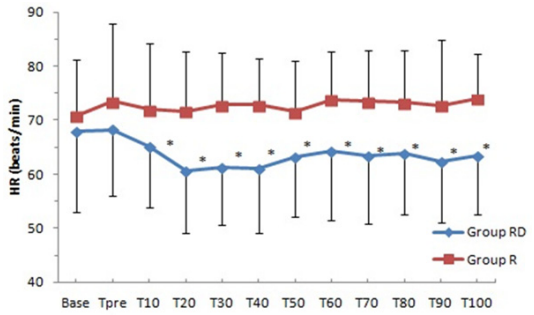

Figure 3. Changes in heart rate in the beach chair position. *P<0.05 compared with Group R. Tpre, before BCP; T_{10}-T_{100}, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 min after BCP. Group RD received 9 mL of ropivacaine (0.75%) with 100 μg of dexmedetomidine for interscalene block. Group R received 1 mL of normal saline instead of dexmedetomidine.

were randomly allocated to two groups. The demographic data were similar between the two groups (**Table 1**). The MAP between the two groups was not significantly different (**Figure 2**). The use of vasopressors was more frequent in Group RD than Group R (23 vs. 11 patients, respectively; P = 0.01). The mean frequency of vasopressor use was 3.7 ± 2.8 and 1.4 ± 2.5, respectively (P = 0.013). The HRs dropped below 50 beats/min in two patients in Group RD and one patient in Group R. However, there was a prompt recovery after atropine administration. The HR was significantly lower in Group RD than Group R during BCP (**Figure 3**). **Figure 4** shows the release of S-100 β after the operation. In Group R, the level of S-100 β, which was 15.13 ± 14.19 pg/ml at admission, was 40.78

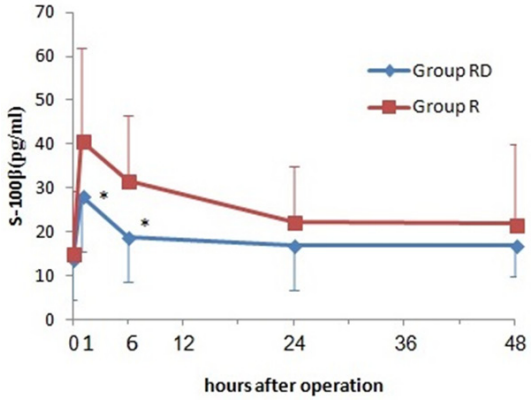

Figure 4. Changes in S-100 β levels. The S-100 β peaked at 1 hour after the operation and then decreased gradually. *P<0.05 compared with Group R. 0, time at admission: Group RD received 9 mL of ropivacaine (0.75%) with 100 μg of dexmedetomidine for interscalene block. Group R received 1 mL of normal saline instead of dexmedetomidine.

± 21.01 pg/ml at 1 hour after surgery. In Group RD, the level of S-100 β, which was 13.74 ± 9.18 pg/ml at admission, was 28.19 ± 12.63 pg/ml at 1 hour after surgery. The S-100 β levels then gradually decreased in both groups until 48 hours after the operation. However, there were significant differences in the change in S-100 β over time between the two groups (repeated-measures ANOVA, P = 0.029). At 1 and 6 hours after the operation, the S-100 β level in Group RD was significantly lower compared with Group R (P = 0.019, 0.002, respectively) (**Figure 4**).

Discussion

Cerebral desaturation and ischemia during shoulder surgery in the BCP have received recent attention and been the subject of controversy. A survey of the American Shoulder and Elbow Surgeons indicated that the rate of stroke during shoulder surgery in the BCP ranged from 0.00382% to 0.000461% [1], which was lower compared to the 0.05% to 7.40% of patients undergoing non-cardiac and non-neurosurgical surgery [12, 13]. However, Pohl and Cullen [3] reported four cases of ischemic brain and spinal cord injury, and Dippmann et al. [4] reported four cases of severe cerebral desaturation after shoulder surgery in the BCP. As these controversial concerns regarding the potential for position-related complications have increased,[5] researchers have recommended more specific monitoring for detecting cerebral desaturation

Table 2. Literature review on S-100 β levels in patients with various conditions

Author Year of publication	Patient state	Time point	S-100 β levels	Unit conversion to pg/ml
Fassbender K et al. [24] 1997	Healthy control group		Not detectable	
	Early ischemia group	4 H-10 H	<0.5 ng/ml	<500 pg/ml
		24 H	>0.5	>500
Rosén H et al. [25] 1998	Healthy blood donor		<0.2 μg/L	<200 pg/ml
	Cardiac arrest	On day 1	11.2 ± 1.1	11200 ± 1100
		On day 2	36.8 ± 1.3	36800 ± 1300
		On day 3	61.5 ± 1.6	61500 ± 1600
Herrmann M et al. [26] 2000	Healthy subject		<0.12 μg/L	<120 pg/ml
	Cardiac surgery	Pre	0.108 ± 0.170	108 ± 170
		1 H	1.859 ± 1.527	1859 ± 1527
		6 H	0.427 ± 0.420	427 ± 420
		20 H	0.210 ± 0.262	210 ± 262
Teepker M et al. [27] 2008	Healthy control group		0.032 ± 0.016 μg/L	32 ± 16 pg/ml
	Patient with migraine	Attack	0.052 ± 0.023	52 ± 23
		Pain-free interval	0.07 ± 0.037	70 ± 37
Duru S et al. [28] 2012	Healthy control group		10.1-22.9 pg/mL	10.1-22.9 pg/mL
	Obstructive sleep apnea syndrome		20.97-230.70	20.97-230.70
Atlas ÖD et al. [29] 2015	Healthy control group		0.08 ± 0.03 μg /L	80 ± 30 pg/ml
	Nontraumatic intracranial hemorrhage	0^{th} day	0.13 ± 0.03	130 ± 30
		5^{th} day	0.13 ± 0.04	130 ± 40
Our result	Group R	Pre	15.13 ± 14.19 pg/mL	15.13 ± 14.19 pg/mL
		1 H	40.78 ± 21.01	40.78 ± 21.01
		6 H	31.67 ± 14.8	31.67 ± 14.8
		24 H	22.20 ± 12.77	22.20 ± 12.77
		48 H	21.75 ± 18.15	21.75 ± 18.15
	Group RD	Pre	13.74 ± 9.18	13.74 ± 9.18
		1 H	28.19 ± 12.63	28.19 ± 12.63
		6 H	18.89 ± 10.46	18.89 ± 10.46
		24 H	16.89 ± 10.12	16.89 ± 10.12
		48 H	16.91 ± 7.09	16.91 ± 7.09

Pre, basal level; H, hours after operation.

events (CDEs) (which cause death of neuronal cells as well as damage to the BBB), strict hemodynamic monitoring for arthroscopic shoulder surgery in the BCP, and correct head positioning [5, 14-19].

Elevated serum S-100 β levels are known to be a sensitive indicator of central nervous system damage and adverse neurological outcomes [20, 21]. S-100 β can leak from structurally damaged nerve cells into cerebrospinal fluid and secondarily across the BBB, but it can also be an indicator of ongoing failure of the BBB without neuroglial damage [8, 22]. In cardiac surgery, S-100 β peaked after cardiopulmonary bypass and gradually decreased over 48 to 72 hours; however, consistently elevated levels or delayed increases were associated with significant neurologic outcomes [7, 8]. Laflam et al. [23] reported that there were no differences in the S-100 β level between baseline and postoperatively in either the lateral decubitus position or BCP among patients undergoing arthroscopic shoulder surgery. However, in the present study in which all patients were positioned in the BCP, the S-100 β level peaked 1 hour postoperatively and gradually decreased over 48 hours.

Westaby et al. [21] found that an S-100 β level of >0.5 μg/L was pathological. When BBB disruption occurred without the presence of neuronal brain damage, S-100 β increased to >0.1 μg/L [22], and after maximal opening of the BBB, it reached the theoretical plateau of 0.34 ng/mL [8]. Technology has elucidated the precise range of detection for S-100 β. In healthy persons, normal S-100 β levels are <120 pg/ml [24]. **Table 2** shows the S-100 β levels in patients with various conditions [24-29]. Thus, in our results, the overall S-100 β levels, including the peak level at 1 hour after surgery [40.78

± 21.01 pg/ml (Group R), 28.19 ± 12.63 pg/ml (Group RD)], were within the normal range. However, it cannot be excluded that the peak elevation of S-100 β may increase beyond the normal range in high-risk patients. The risk factors for CDEs during shoulder arthroscopy in the BCP have yet to be established. However, Bokor et al. [19] identified such risk factors as follows: those with an elevated BCP and body mass index (BMI) of >34 kg/m^2 are considered high risk, and those with diabetes mellitus, obstructive sleep apnea, hypertension (perioperative β-blockade may double the risk of stroke), and a history of stroke are considered low risk. Salazar et al. [18] found that an increased BMI was a statistically significant risk factor for CDEs.

Peripheral nerve blocks are used as an adjuvant to general anesthesia for postoperative analgesia. Perineural DEX is a potential local anesthetic adjuvant that has a facilitatory effect when administered as part of a brachial plexus block without hypotension [30]. In contrast to perineural DEX, intravenous DEX causes hypotension and bradycardia. Recently, DEX has been shown to attenuate ischemia-reperfusion injury, and treatment with DEX may be a clinical method for spinal cord protection [11, 31]. In addition, DEX exhibits neuroprotective effects against neonatal glutamate-induced injury, which is a leading cause of neuronal cell death in the human brain, via an increase in brain-derived neurotrophic factor [10]. In our study, patients who were administered perineural DEX showed similar but down-shifted S-100 β release patterns during the acute postoperative period according to time course. Although few studies have explored the effect of DEX on S-100 β, our study showed that S-100 β release was suppressed by perineural DEX.

This study had some limitations. First, no neurocognitive function test after the operation was performed. We only evaluated the patients according to whether or not clinical neurologic change occurred until discharge. Second, the dose of DEX for interscalene block was not titrated by each patient's body weight. Although the dose relationships between perineural DEX and hemodynamic effects are not known [9], titration of the dose of DEX by body weight may have reduced the use of vasopressors in Group RD. Third, cerebral oxygenation was not monitored during anesthesia. Combined monitoring of cerebral oxygenation and blood pressure can help to detect and reverse CDEs and minimize the risk of neurocognitive dysfunction, thereby improving patient safety [18, 32].

Conclusions

S-100 β was elevated over two-fold at 1 hour after arthroscopic shoulder surgery in the BCP and decreased gradually during the postoperative period, but it still remained within the normal range. Perineural DEX suppressed the release of serum S-100 β and may be protective agent against cerebral ischemic changes in high-risk patients undergoing arthroscopic shoulder surgery in the BCP.

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Disclosure of conflict of interest

None.

Address correspondence to: Sung-Mi Hwang, Department of Anesthesiology and Pain Medicine, Chuncheon Sacred Heart Hospital, 77 Sakju-ro, Chuncheon-si, Gangwon-do, 200-704, Korea. Tel: +82-33-240-5155; Fax: +82-33-252-0941; E-mail: h70sm@hallym.or.kr

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