·老年患者围术期管理专栏·

小剂量右美托咪定对既往脑卒中老年患者术后谵妄发生率的影响:对随机对照研究数据的二次分析

许珍真,苏 仙,孟昭婷,吴新海,崔 凡,朱赛楠,王东信*
(北京大学第一医院麻醉科,北京 100034)

【摘 要】 **目的** 观察预防性小剂量右美托咪定输注对既往脑卒中老年患者术后谵妄发生率的影响。**方法** 161例既往合并脑卒中病史、术后入重症监护病房(ICU)的老年(≥65岁)患者,从入ICU起到术后次日晨随机接受小剂量右美托咪定[0.1 μg/(kg·h),右美托咪定组,$n=82$]或安慰剂(生理盐水)(对照组,$n=79$)持续输注。采用ICU意识模糊评估法每日2次评估术后7 d内谵妄发生情况。**结果** 术后7 d内谵妄发生率右美托咪定组(12例,14.6%)明显低于对照组(23例,29.1%,$P=0.026$)。采用logistic回归分析校正混杂因素后,小剂量右美托咪定输注仍然是术后谵妄风险降低的独立影响因素(OR=0.36,95% CI 0.15~0.89,$P=0.027$)。试验药物输注期间低血压发生率右美托咪定组(35例,42.7%)明显高于对照组(19例,24.1%,$P=0.012$),但低血压干预的患者比例两组间无明显差异。**结论** 对于既往合并脑卒中、术后进入ICU的老年患者,术后预防性输注小剂量右美托咪定可以降低术后谵妄的发生,但需监测低血压的发生情况。

【关键词】 右美托咪定;既往脑卒中;老年人;术后谵妄
【中图分类号】 R592;R969 【文献标识码】 A 【DOI】 10.11915/j.issn.1671-5403.2017.02.023

Effects of low-dose dexmedetomidine on postoperative delirium incidence in the elderly with a history of cerebral stroke: a secondary analysis based on a random clinical trial

XU Zhen-Zhen, SU Xian, MENG Zhao-Ting, WU Xin-Hai, CUI Fan, ZHU Sai-Nan, WANG Dong-Xin*
(Department of Anesthesiology, Peking University First Hospital, Beijing 10034, China)

【**Abstract**】 **Objective** To determine the effect of preventative infusion of low-dose dexmedetomidine (DEX) on the incidence of postoperative delirium among the elderly patients with a history of cerebral stroke. **Methods** Based on our previous random, double-blind, pracebo control study, a total of 161 elderly patients (≥65 years old) with a history of cerebral stroke who were admitted to the intensive care unit (ICU) of our hospital after surgery from May 2011 to November 2013 were enrolled in this study. They were randomly assigned into DEX group [an infusion of 0.1 μg/(kg·h) DEX, $n=82$] and placebo group (saline, $n=79$) in the morning from the second day after operation. Delirium was assessed twice daily with the Confusion Assessment Method for the ICU (CAM-ICU) within 7 d after surgery. **Results** The incidence of postoperative delirium was significantly lower in the DEX group than the placebo group [12/82 (14.6%) *vs* 23/79 (29.1%), $P=0.026$]. After adjustment of confounding factors, multivariate logistic regression analysis showed that low-dose DEX infusion was an independent influencing factor for postoperative delirium (OR=0.36, 95% CI: 0.15–0.89, $P=0.027$). But the occurrence of hypotension was obviously higher in the DEX group than in the placebo group [42.7% (35/82) *vs* 24.1% (19/79), $P=0.012$], but no such difference was found between those who had the hypotension intervention from the 2 groups. **Conclusion** For the elderly patients with a history of cerebral stroke and transferred to ICU after surgery, postoperative prophylactic infusion of low-dose DEX could reduce the incidence of postoperative delirium, but hypotension should be monitored in the duration.

【**Keywords**】 dexmedetomidine; history of cerebral stroke; aged; postoperative delirium
Corresponding author: *WANG Dong-Xin*, *Email*: *wangdongxin@hotmail.com*

收稿日期:2016-10-08;**修回日期**:2016-11-28
通信作者:王东信,E-mail:wangdongxin@hotmail.com

谵妄(delirium)是老年患者术后常见的并发症[1,2],尤其多见于既往合并脑卒中的老年患者[3-5]。谵妄的发生伴随预后恶化,包括并发症增多、住院时间延长、功能恢复延迟和死亡率升高[6-8]。因此,预防谵妄发生是老年患者围术期管理的重要内容。右美托咪定(dexmedetomidine)是一种高选择性α2受体激动剂,具有镇静、抗焦虑和镇痛作用。研究显示,右美托咪定用于重症监护病房(intensive care unit, ICU)机械通气患者镇静可缩短机械通气时间、缩短ICU停留时间、减少谵妄发生[9-11]。最近的一项随机对照研究结果显示,老年患者术后预防性给予小剂量右美托咪定可减少谵妄的发生[12]。据此推测小剂量右美托咪定对既往合并脑卒中的老年患者也有预防术后谵妄发生的作用。本研究的目的是明确右美托咪定对既往脑卒中患者术后谵妄发生率的影响。

1 对象与方法

本研究是对我们前期随机、双盲、安慰剂对照研究结果的二次分析[12]。研究方案获得医院临床研究伦理委员会批准(2011[10]),并在中国临床研究注册网站注册(编号ChiCTR-TRC-10000802)。所有入组患者均由本人或其家属签署了知情同意书。

1.1 研究对象

本研究收集2011年5月至2013年11月于北京大学第一医院和第三医院外科手术后收住ICU的患者。纳入标准:(1)年龄≥65岁(且<90岁);(2)手术3个月前有明确诊断的脑卒中病史;(3)全身麻醉下接受择期非心脏手术;(4)手术当日进入ICU。排除标准(受试者存在下列任何一种情况即不能纳入本研究):(1)术前患有精神分裂症、癫痫、帕金森症、重症肌无力者;(2)术前因昏迷、严重痴呆或语言障碍而无法交流者;(3)术前存在严重心脏(NYHA分级>Ⅲ级或LVEF<30%)、肝脏(Child-Pugh C级)或肾脏(术前接受透析)功能异常者;(4)颅脑损伤或神经外科手术术后患者。

1.2 方法

所有患者术中均采用全身麻醉,具体用药由麻醉实施者决定,但避免使用东莨菪碱、长托宁和右美托咪定,阿托品仅用于治疗心动过缓;术后尽可能实施患者自控镇痛。

患者入ICU后,先进行Richmond躁动镇静评分(Richmond agitation-sedation scale, RASS)分级[13],RASS评分≥-2分时右美托咪定组患者给予右美托咪定静脉输注0.1 μg/(kg·h)至术后第1天上午8:00,对照组以与右美托咪定组相同的时间和速度静脉输注生理盐水。在ICU停留期间,两组患者均可根据需要给予丙泊酚、咪达唑仑和吗啡作为镇静、镇痛药物。其他治疗均按照临床常规进行。

术后前7天每日2次(分别于8:00~12:00 am和18:00~20:00 pm两个时间段)使用ICU意识模糊评估法(confusion assessment method for the ICU, CAM-ICU)[14]评估术后7 d谵妄的发生情况并记录相关治疗措施及干预。术后24 h内使用数字分级量表评估疼痛严重程度(0=完全不痛,10=最严重疼痛);术后1~3 d采用数字分级量表评估主观睡眠质量(0=最佳睡眠,10=最差睡眠);术后前7 d每日评估非谵妄并发症发生情况,以后每周1次随访,直至术后30 d。记录术后机械通气时间、ICU停留时间、术后住院时间和术后30 d死亡率。本研究主要观察结局是术后7 d谵妄发生率;次要结局是术后外科并发症发生率、机械通气时间、ICU停留时间(截止至术后30 d)和术后30 d死亡率。

术前评估和术后随访均由培训合格的研究者完成,进行术后谵妄随访的研究者均经过CAM-ICU谵妄评估的专业精神科医师培训。CAM-ICU检测4个方面的谵妄临床特征,包括(1)精神状态的急性变化或波动;(2)注意力不集中;(3)思维无序;(4)意识水平异常。谵妄的诊断需要同时具备特征1、2,以及特征3或4。

1.3 统计学处理

采用SPSS21.0软件对数据进行统计学处理。连续变量及等级资料的分析采用两独立样本t检验或Mann-Whitney U检验;分类变量的分析采用卡方检验或Fisher精确概率法;时间相关事件变量采用Kaplan-Meier生存分析,组间差异使用Log-Rank法进行检验。单因素分析得到的有统计学差异的因素($P<0.10$)代入logistic多因素回归模型中以确定术后谵妄的独立危险因素。以$P<0.05$为差异有统计学意义。

2 结 果

2.1 一般资料比较

本研究入组161例既往合并脑卒中的老年患者,其中对照组79例,右美托咪定组82例。术后前7 d使用咪达唑仑的患者比例右美托咪定组(4例)明显少于对照组(13例)(4.9% *vs* 16.5%,$P=0.017$),其他基础情况和围术期情况两组间差异无统计学意义(表1,2)。

表 1 基线资料比较

Table 1 Comparison of baseline data between two groups

Item	Control group (n = 79)	Dexmedetomidine group (n = 82)	P value
Age (years, $\bar{x} \pm s$)	76 ± 7	74 ± 6	0.086
Male [n (%)]	60 (75.9)	47 (57.3)	0.066
BMI (kg/m^2, $\bar{x} \pm s$)	23.9 ± 4.2	24.3 ± 4.0	0.457
Education duration (years, $\bar{x} \pm s$)	8.71 ± 4.71	8.90 ± 5.38	0.809
Comorbidity [n (%)]			
Hypertension	62 (78.5)	62 (75.6)	0.665
Coronary heart disease	33 (41.8)	32 (39.0)	0.423
COPD	5 (6.3)	10 (12.2)	0.200
Diabetes mellitus	28 (35.4)	28 (34.1)	0.863
Insulin treatment	12 (15.2)	15 (18.3)	0.598
Kidney dysfunction *	5 (6.3)	4 (4.9)	0.954
ASA class [n (%)]			0.263
Ⅱ	35 (44.3)	29 (35.4)	–
Ⅲ	44 (55.7)	53 (64.6)	–

BMI: body mass index; COPD: chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists. * Serum creatinine > 177 μmol/L

表 2 围术期情况比较

Table 2 Comparison of perioperative variables between two groups

Item	Control group (n = 79)	Dexmedetomidine group (n = 82)	P value
Type of anesthesia [n (%)]			0.861
General	71 (89.9)	73 (89)	–
Combined epidural-general	8 (10.1)	9 (11)	–
Duration of anesthesia (h, $\bar{x} \pm s$)	4.81 ± 2.46	4.84 ± 2.15	0.920
Type of surgery [n (%)]			0.410
Intra-abdominal	49 (62.0)	55 (67.1)	–
Intra-thoracic	11 (13.9)	9 (11.0)	–
Spinal and extremital	10 (12.7)	5 (6.1)	–
Superficial and transurethral	9 (11.4)	13 (5.9)	–
Patients with endotracheal intubation on ICU admission [n (%)]	45 (57.0)	47 (57.3)	0.964
APACHE Ⅱ score on ICU admission [M (Q_1, Q_3)]	10 (8, 12)	10 (8, 12)	0.368
Postoperative analgesia [n (%)]			0.782
None	8 (10.1)	11 (13.4)	–
Patient-controlled intravenous analgesia	64 (81.0)	63 (76.8)	–
Patient-controlled epidural analgesia	7 (8.9)	8 (9.8)	–
Use of other analgesics or sedatives during the first 7 postoperative days [n (%)]			
Propofol	41 (51.9)	43 (52.4)	0.945
Flurbiprofen axetil	27 (34.2)	25 (30.5)	0.617
Morphine	23 (29.1)	31 (37.8)	0.243
Midazolam	13 (16.5)	4 (4.9)	0.017

ICU: intensive care unit; APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Ⅱ score

2.2 术后谵妄事件独立危险因素分析

术后 7 d 内谵妄发生率右美托咪定组明显低于对照组(14.6% *vs* 29.1%, P = 0.026; 表 3)。单因素 logistic 回归分析筛选出 7 项术后谵妄的影响因素,包括体质量指数(body mass index, BMI)、术前美国麻醉医师协会(American Society of Anesthesiologists, ASA)分级、恶性肿瘤、带管入 ICU、入选右美托咪定组和术后使用咪达唑仑;校正混杂因素的作用后,进入右美托咪定组(OR = 0.36, 95% CI 0.15 ~ 0.89, P = 0.027)仍然是术后谵妄风险降低的独立影响因素(表 3)。

2.3 两组患者有效性结局比较

带管患者术后拔管时间、术后非谵妄并发症发生率、ICU 停留时间、再次入 ICU 率、术后 7 d 内出院率、术后住院时间和 30 d 全因死亡率两组间均无明显差异。术后当天 3, 6, 24 h 的静息和活动时疼痛数字评分(numerical rating score, NRS)两组间也无明显差异,但术后第 1、3 天的主观睡眠质量评分

右美托咪定组明显低于(即优于)对照组(表4)。

2.4 两组患者不良事件发生率情况比较

试验药物输注结束时RASS评分两组差异无统计学意义。试验药物输注期间低血压发生率右美托咪定组明显高于对照组[42.7% *vs* 24.1%, $P=0.012$],但低血压干预的患者比例两组间无明显差异;其他不良事件发生率、不良事件干预比例及试验药物调整比例两组间均无明显差异(表5)。

3 讨 论

既往脑卒中患者是术后谵妄的高危人群[15]。随着我国人口老龄化的加剧,脑血管病患者逐年增加,这给外科患者的围术期管理带来挑战。但至今未有针对既往脑卒中患者外科手术后谵妄预防的相关研究。本研究结果显示,对于既往合并脑卒中的老年患者,预防性输注小剂量右美托咪定可减少术后7 d内谵妄的发生率。

以往的研究显示右美托咪定用于ICU机械通气患者镇静可减少谵妄的发生[9,10,16,17]。但这些研究中右美托咪定都是与传统的镇静(如咪达唑仑或丙泊酚)或镇痛(阿片类)药物相比较。由于传统的镇静、镇痛药物本身即具有增加谵妄发生风险的作用[18],因此这些结果并不能证明右美托咪定"预防"了谵妄的发生,可能仅仅是未增加谵妄的发生。本研究中有将近半数患者不需要机械通气,因此干预组采用了"亚镇静"剂量的右美托咪定,而对照组采用了安慰剂(生理盐水)。本研究中两组患者在试验药物输注结束时的RASS评分相似,说明右美托

表3 术后谵妄预测因素logistic回归分析

Table 3 Risk factors of postoperative delirium by logistic regression analysis

Item	Univariate analysis (P value)	Multivariate analysis	
		OR(95% CI)	P value
BMI	0.002	0.85(0.76-0.95)	0.005
Preoperative ASA class (class Ⅲ to Ⅱ)	0.059	1.72(0.67-4.41)	0.262
Malignancy	0.096	0.71(0.28-1.76)	0.454
Patients with endotracheal intubation on ICU admission	0.057	1.79(0.73-4.41)	0.204
APACHE Ⅱ score on ICU admission	0.010	1.11(0.99-1.24)	0.067
Dexmedetomidine use	0.028	0.36(0.15-0.89)	0.027
Postoperative midazolam use	0.047	1.03(0.25-4.32)	0.964

BMI: body mass index; ASA: American Society of Anesthesiologists; ICU: intensive care unit; APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Ⅱ score

表4 患者结局比较

Table 4 Comparison of outcomes between two groups

Item	Control group ($n=79$)	Dexmedetomidine group ($n=82$)	P value
Overall incidence of delirium[n(%)]	23(29.1)	12(14.6)	0.026
Time to extubation [h, M(Q_1,Q_3)]*	7.67(3.25,11.58)	4.17(2.25,13.00)	0.363
Overall incidence of non-delirium complications[n(%)]	16(20.3)	16(19.5)	0.906
Length of ICU stay [h, M(Q_1,Q_3)]	21(18,40)	22(19,43)	0.368
Length of hospital stay after surgery [d, M(Q_1,Q_3)]	11(7,15)	10(7,16)	0.938
All-cause 30-day mortality [n(%)]	0(0.0)	1(1.2)	>0.999
NRS for pain at rest [M(Q_1,Q_3)]			
3 h after surgery	2(0,4)	2(1,3)	0.708
6 h after surgery	2(0,3)	1(0,2)	0.170
24 h after surgery	2(0,3)	1(0,2)	0.616
NRS for pain with movement [M(Q_1,Q_3)]			
3 h after surgery	3(1,5)	3(2,5)	0.879
6 h after surgery	3(1,4)	2(1,4)	0.504
24 h after surgery	3(1,3)	2(1,3)	0.440
NRS for subjective sleep quality [M(Q_1,Q_3)]			
First morning after surgery	4(2,6)	2(0,4)	<0.001
Second morning after surgery	4(2,5)	3(1,6)	0.408
Third morning after surgery	3(2,5)	2(1,4)	0.030

NRS: numerical rating score; ICU: intensive care unit. * Time from patients who had received ventilation therapy

表 5 不良事件发生情况比较

Table 5 Comparison of adverse events between two groups

Item	Control group (n = 79)	Dexmedetomidine group (n = 82)	P value
RASS score at the end of drug infusion [median (full range)]	0(−1 to 0)	0(−1 to 0)	0.810
Adverse event[n(%)]			
Bradycardia *	11(13.9)	17(20.7)	0.255
Bradycardia with intervention	0(0.0)	2(2.4)	0.497
Hypotension #	19(24.1)	35(42.7)	0.012
Hypotension with intervention	12(15.2)	15(18.3)	0.598
Tachycardia △	14(17.7)	8(9.8)	0.141
Tachycardia with intervention	5(6.3)	3(3.7)	0.490
Hypertension ▲	16(20.3)	10(12.2)	0.165
Hypertension with intervention	16(20.3)	20(24.4)	0.529
Hypoxemia ☆	9(11.4)	6(7.3)	0.374
Hypoxemia with intervention	1(1.3)	0(0.0)	0.491
Modification of drug infusion[n(%)]			0.275
None	75(94.9)	71(86.6)	–
Infusion rate decreases temporarily	1(1.3)	3(3.7)	–
Infusion stops temporarily	3(3.8)	7(8.5)	–
Infusion stops permanently	0(0.0)	1(1.2)	–

RASS: Richmond agitation-sedation scale. Interventions for bradycardia, tachycardia, and hypertension include adjustment of drug infusion and/or other clinical therapy, such as fluid therapy, medication, adjustment of ventilator setting or physiotherapy. * Heart rate <55 beats/min or decreases by over 20% from baseline; # blood pressure <95 mmHg or decreases by over 20% from baseline; △ heart rate >100 beats/min or increases by over 20% from baseline; ▲ blood pressure >160 mmHg or increases by over 20% from baseline; ☆ pulse oxygenation saturation <90% or decreases by over 5% from baseline

咪定确实未产生明显的镇静作用;虽然右美托咪定组有更少患者术后使用了咪达唑仑(可能与右美托咪定的使用有关,但需要进一步研究确认),但校正混杂因素后右美托咪定的使用仍然明显减少了谵妄发生。说明小剂量右美托咪定确实对既往脑卒中患者起到了预防术后谵妄的作用。

右美托咪定预防术后谵妄的作用机制还不完全清楚。在以往的研究中,镇静剂量的右美托咪定用于机械通气患者可在一定程度上改善睡眠结构[19]。我们最近的研究显示,对于术后不需要机械通气的 ICU 患者,“亚镇静”剂量右美托咪定输注也能在一定程度上改善睡眠结构,表现为 1 期非快动眼睡眠(即浅睡眠)减少、2 期非快动眼睡眠增加和主观睡眠质量改善[20]。在我们另一项大样本量的随机对照研究中,小剂量右美托咪定输注在改善主观睡眠质量和减少术后谵妄发生方面的作用在时间上是一致的[12]。与我们前期的研究不同,本研究并未发现右美托咪定改善术后镇痛效果,可能与右美托咪定剂量小、作用弱及病例数少有关。但本研究同样发现小剂量右美托咪定改善了术后主观睡眠质量。综合以上结果,小剂量右美托咪定可能通过改善睡眠质量而减少了术后谵妄的发生,但这仍然需要进一步的研究证实。此外,研究显示右美托咪定可降低围术期应激反应程度[21,22],并对缺血再灌注脑产生保护作用[23-25],可能也在谵妄预防中发挥了作用。

本研究中试验药物输注期间右美托咪定组低血压的发生率明显高于对照组,心动过缓的发生率略高于对照组,但差异无统计学意义。需要说明的是,与以往研究相比,本研究中不良事件的诊断采用了更为宽松的诊断标准,如本研究中诊断标准低血压为收缩压 <95 mmHg 或较基础值降低 20%,心动过缓为心率 <55 beats/min 或较基础值降低 20%;而 Riker 等[10] 研究中相应的诊断标准分别为收缩压 <80 mmHg或较基础值降低超过 30%,心率 <40 beats/min或较基础值降低 30%。另外,本研究需要进行不良事件干预的患者比例两组间相似。说明小剂量右美托咪定输注的安全性是可接受的,但需关注并进行监护。

除二次分析本身的特点外,本研究还有一些局限性:(1)未收集脑卒中的具体分型和发病时间,因此不能除外不同类型脑卒中及脑卒中发病时间对研究结果的影响;(2)只观察了术后进入 ICU 的患者,右美托咪定对非 ICU 患者术后谵妄的影响仍有待探索;(3)样本量较小。尽管如此,本研究是右美托咪定在既往脑卒中患者术后谵妄预防方面的首次探索,具有很好的参考意义。

综上所述,对于既往合并脑卒中、术后进入 ICU 的老年患者,术后当日预防性输注小剂量右美托咪定可以降低术后谵妄的发生,但需监测低血压的发生情况。

【参考文献】

[1] Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability [J]. JAMA, 1996, 275(11): 852-857.

[2] Inouye SK. Delirium in hospitalized older patients [J]. Clin Geriatr Med, 1998, 14(4): 745-764.

[3] Shi CM, Wang DX, Chen KS, *et al*. Incidence and risk factors of delirium in critically ill patients after non-cardiac surgery [J]. Chin Med J (Engl), 2010, 123(8): 993-999. DOI: 10.3760/cma. j. issn. 0366-6999. 2010. 08. 004.

[4] Luger MF, Muller S, Kammerlander C, *et al*. Predictors of postoperative cognitive decline in very old patients with hip fracture: a retrospective analysis [J]. Geriatr Orthop Surg Rehabil, 2014, 5(4): 165-172. DOI: 10.1177/2151458514548577.

[5] Guo Y, Jia P, Zhang J, *et al*. Prevalence and risk factors of postoperative delirium in elderly hip fracture patients [J]. J Int Med Res, 2016, 44(2): 317-327. DOI: 10.1177/0300060515624936.

[6] Lat I, McMillian W, Taylor S, *et al*. The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients [J]. Crit Care Med, 2009, 37(6): 1898-1905. DOI: 10.1097/CCM.0b013e31819ffe38.

[7] Quinlan N, Rudolph JL. Postoperative delirium and functional decline after noncardiac surgery [J]. J Am Geriatr Soc, 2011(59): S301-S304. DOI: 10.1111/j. 1532-5415. 2011. 03679. x.

[8] Abelha FJ, Luis C, Veiga D, *et al*. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery [J]. Crit Care, 2013, 17(5): 1-10. DOI: 10.1186/cc13084.

[9] Pandharipande PP, Pun BT, Herr DL, *et al*. Effect of sedation with dexmedetomidine *vs* lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial [J]. JAMA, 2007, 298(22): 2644-2653. DOI: 10.1001/jama.298.22.2644.

[10] Riker RR, Shehabi Y, Bokesch PM, *et al*. Dexmedetomidine *vs* midazolam for sedation of critically ill patients: a randomized trial [J]. JAMA, 2009, 301(5): 489-499. DOI: 10.1001/jama.2009.56.

[11] Keating GM. Dexmedetomidine: a review of its use for sedation in the intensive care setting [J]. Drugs, 2015, 75(10): 1119-1130. DOI: 10.1007/s40265-015-0419-5.

[12] Su X, Meng ZT, Wu XH, *et al*. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial [J]. Lancet, 2016, 388(10054): 1893-1902. DOI: 10.1016/S0140-6736(16)30580-3.

[13] Sessler CN, Gosnell MS, Grap MJ, *et al*. The Richmond Agitation-Sedation Scale — Validity and reliability in adult intensive care unit patients [J]. Am J Respir Crit Care Med, 2002, 166(10): 1338-1344. DOI: 10.1164/rccm.2107138.

[14] Ely EW, Inouye SK, Bernard GR, *et al*. Delirium in mechanically ventilated patients — validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU) [J]. JAMA, 2001, 286(21): 2703-2710.

[15] Otomo S, Maekawa K, Goto T, *et al*. Pre-existing cerebral infarcts as a risk factor for delirium after coronary artery bypass graft surgery [J]. Interact Cardiovasc Thorac Surg, 2013, 17(5): 799-804. DOI: 10.1093/icvts/ivt304.

[16] Xia ZQ, Chen SQ, Yao X, *et al*. Clinical benefits of dexmedetomidine *versus* propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials [J]. J Surg Res, 2013, 185(2): 833-843. DOI: 10.1016/j. jss. 2013. 06. 062.

[17] Lin YY, He B, Chen J, *et al*. Can dexmedetomidine be a safe and efficacious sedative agent in post-cardiac surgery patients? a meta-analysis [J]. Crit Care, 2012, 16(5): 1-11. DOI: 10.1186/cc11646.

[18] Reade MC, Finfer S. Sedation and delirium in the intensive care unit [J]. N Engl J Med, 2014, 370(5): 444-454. DOI: 10.1056/NEJMra1208705.

[19] Alexopoulou C, Kondili E, Diamantaki E, *et al*. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study [J]. Anesthesiology, 2014, 121(4): 801-807. DOI: 10.1097/ALN.0000000000000361.

[20] Wu XH, Cui F, Zhang C, *et al*. Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial [J]. Anesthesiology, 2016, 12(5): 979-991. DOI: 10.1097/ALN. 0000000000001325.

[21] 郎 宇, 王天龙. 右美托咪定在老年麻醉中的应用及进展[J]. 中国新药杂志, 2013, 4: 438-442.
Lang Y, Wang TL. Application and advance of dexmedetomidine anesthesia in the elderly [J]. Chin J New Drugs, 2013, 4: 438-442.

[22] 程东群, 胡明泰, 黄雯静. 右美托咪定监测麻醉复合局部麻醉在高龄患者疝修补术中的临床应用[J]. 中华老年多器官疾病杂志, 2016, 15(1): 29-33. DOI: 10.11915/j. issn. 1671-5403. 2016. 01. 007.
Cheng DQ, Hu MT, Huang WJ. Clinical application of dexmedetomidine in monitored anesthesia care for inguinal hernioplasty under local anesthesia in elderly patients [J]. Chin J Mult Organ Dis Elderly, 2016, 15(1): 29-33. DOI: 10.11915/j. issn. 1671-5403. 2016. 01. 007.

[23] Ma D, Hossain M, Rajakumaraswamy N, *et al*. Dexmedetomidine produces its neuroprotective effect via the alpha 2A-adrenoceptor subtype [J]. Eur J Pharmacol, 2004, 502(1,2): 87-97. DOI: 10.1016/j. ejphar. 2004. 08. 044.

[24] Ma D, Rajakumaraswamy N, Maze M. Alpha2-adrenoceptor agonists: shedding light on neuroprotection [J]? Br Med Bull, 2004, 71(1): 77-92. DOI: 10.1093/bmb/ldh036.

[25] Yan M, Dai H, Ding T, *et al*. Effects of dexmedetomidine on the release of glial cell line-derived neurotrophic factor from rat astrocyte cells [J]. Neurochem Int, 2011, 58(5): 549-557. DOI: 10.1016/j. neuint. 2011. 01. 013.

(编辑: 王雪萍)