

A National Multicenter Survey on Management of Pain, Agitation, and Delirium in Intensive Care Units in China

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Abstract

Background: The management of pain, agitation, and delirium (PAD) in Intensive Care Unit (ICU) is beneficial for patients and makes it widely applied in clinical practice. Previous studies showed that the clinical practice of PAD in ICU was improving; yet relatively little information is available in China. This study aimed to investigate the practice of PAD in ICUs in China.

Methods: A multicenter, nationwide survey was conducted using a clinician-directed questionnaire from September 19 to December 18, 2016. The questionnaire focused on the assessment and management of PAD by the clinicians in ICUs. The practice of PAD was compared among the four regions of China (North, Southeast, Northwest, and Southwest). The data were expressed as percentage and frequency. The Chi-square test, Fisher's exact test, and line-row Chi-square test were used.

Results: Of the 1011 valid questionnaire forms, the response rate was 80.37%. The clinicians came from 704 hospitals across 158 cities of China. The rate of PAD assessment was 75.77%, 90.21%, and 66.77%, respectively. The rates of PAD scores were 45.8%, 68.94%, and 34.03%, respectively. The visual analog scale, Richmond agitation-sedation scale, and confusion assessment method for the ICU were the first choices of scales for PAD assessment. Fentanyl, midazolam, and dexmedetomidine were the first choices of agents for analgesic, sedation, and delirium treatment. While choosing analgesics and sedatives, the clinicians put the pharmacological characteristics of drugs in the first place (66.07% and 76.36%). Daily interruption for sedation was carried out by 67.26% clinicians. Most of the clinicians (87.24%) used analgesics while using sedatives. Of the 738 (73%) clinicians titrating the sedatives on the basis of the proposed target sedation level, 268 (26.61%) clinicians just depended on their clinical experience. Totally, 519 (51.34%) clinicians never used other nondrug strategies for PAD. The working time of clinicians was an important factor in the management of analgesia and sedation rather than their titles and educational background. The ratios of pain score and sedation score in the Southwest China were the highest and the North China were the lowest. The ratios of delirium assessment and score were the same in the four regions of China. Moreover, the first choices of scales for PAD in the four regions were the same. However, the top three choices of agents in PAD treatment in the four regions were not the same.

Conclusions: The practice of PAD in China follows the international guidelines; however, the pain assessment should be improved. The PAD practice is a little different across the four regions of China; however, the trend is consistent.

Trial Registration: The study is registered at <http://www.clinicaltrials.gov> (No. ChiCTR-OOC-16009014, www.chictr.org.cn/index.aspx).

Key words: Agitation; Delirium; Intensive Care Unit; Pain; Sedation

INTRODUCTION

The role of sedatives for patients in Intensive Care Units (ICUs) has been well recognized for more than 50 years. They reduce the adverse stimulus in both physiological and psychological aspects,^[1] improve the short- and long-term outcomes, optimize the resource use,^[2-4] and so on. On the basis of increasing studies and evidence, the guideline was

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Received: 30-01-2017 **Edited by:** Peng Lyu

How to cite this article: Wang J, Peng ZY, Zhou WH, Hu B, Rao X, Li JG. A National Multicenter Survey on Management of Pain, Agitation, and Delirium in Intensive Care Units in China. *Chin Med J* 2017;130:1182-8.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.205852

updated and more clinical practices were recommended to the clinicians in ICUs,^[5] for example, routine monitoring of pain, considering opioids as the first-line choice of analgesics, monitoring the depth of sedation, maintaining a light level rather than a deep level of sedation, and routine monitoring of delirium. Moreover, Prof. Shehabi^[6] emphasized the importance of early goal-directed sedation. Recently, Vincent *et al.*^[7] advised that the sedation practices should be guided by the early comfort using analgesia, minimal sedatives, and maximal humane care concept.

However, the practice usually even lags behind the evidence. The application of international guidelines was still at a low rate.^[8] It needed eligible training that seemed generally scarce. Recently, some surveys showed that^[9-11] a number of patients in the ICUs still suffered from pain and inappropriate sedation treatment, and the rate of delirium assessment was still low. About 10 years ago, some surveys showed that^[1,12] most of the patients did not get enough treatment for pain, agitation, and delirium (PAD) in China. However, from then on, no relevant research has been published. Until now, the status of PAD management in ICUs in China is unknown, and no Chinese sedation guideline is available for intensivists. The updated guideline and recommendations were based on the researches of clinical practice and problems. Therefore, PAD surveys were always traced by different countries. The application of the guideline was effectively proved through the results of the investigation, and new problems encountered were updated in the guideline. The present practice of PAD management in China needs to be investigated to clarify whether Chinese clinicians follow the international guidelines and also the different situations in China. Therefore, the present study aimed to investigate the practice of PAD management in ICUs in China using a nationwide survey.

METHODS

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki*. The study was approved by the Ethics Committees of the Zhongnan Hospital, Wuhan University, China (No. 2016083). Written informed consent was obtained from all participants.

Study design and participants

This multicenter, nationwide survey was conducted from September 19 to December 18, 2016. Of 30 province-level administrations were included in this study. According to the list of members of the standing committees of the intensive medical branch of Chinese Medical Association, a coordinator in every province was chosen to send the questionnaire forms to the clinicians working in the ICUs in the range of a province. They distributed the questionnaire forms as broadly as possible by considering the hospital level, location of the hospital, and clinicians' information. The list of all respondents who received questionnaire forms was recorded and tracked by the coordinators. The clinician who did not submit the questionnaire form after reminding twice was

regarded as no response. Moreover, according to the traditional geographical regions, the study zones were divided into six-region partitions: North, Northeast, Northwest, East, South central, and Southwest. According to the similar economic developments and other features, the regions were combined as follows: North (R1), Southeast (R2), Northwest (R3), and Southwest (R4)^[13] [Figure 1]. Comparisons of the four regions were made to offer the important information on differences in the PAD practice status.

Survey design

The survey was conducted in the form of a self-administered questionnaire. The questionnaire was designed by the study group consisting of professors in ICUs and the teaching and research sections of epidemiology and health statistics. The reference materials included the guidelines,^[5,14] previous surveys in other countries^[8,15-20] in the field of PAD, and the recommendations for survey methodology.^[21] When the final version of the questionnaire was completed, the data were changed to electrical versions [Supplementary material]. Then, the questionnaire forms were distributed to participants through the two-dimensional code or the website. When the questionnaire forms were submitted, all answers and data were preserved automatically.

Trial registry

The study was registered in the Chinese Clinical Trial Registry and had a registration number. This survey investigated the clinicians. All clinicians were anonymous and expected to fulfill the questionnaire forms by themselves if they were willing to participate in this study. The results of the study were used for the medical research, and no individual information was exposed.

Statistical analysis

All data from the valid questionnaire forms were analyzed using the Statistical Package for Social Sciences (SPSS version 24.0, IBM, NY, USA). Categorical variables were expressed as frequencies and percentages. The categorical variables were analyzed using the Chi-square test or Fisher's exact test. The Bonferroni test was used for comparison among groups (subdividing by row column table). The equation used was $a' = a/(k[k-1]/2)$ (where k is the number of groups; $a = 0.05$; therefore, $P < 0.0083$ was considered statistically significant). The constituent ratio was also compared using the line-row Chi-square test. All tests of significance were two tailed, and a value of $P < 0.05$ was considered statistically significant.

RESULTS

Response rate and demographics

A total of 1258 questionnaire forms were distributed, and the responses were received from the clinicians in general ICUs. In the process of data collection, responses in 238 questionnaire forms were incomplete and hence excluded, and those in 9 questionnaire forms were from clinicians at Pediatric ICU. As a result, 1011 valid questionnaire forms were analyzed. The response rate was

80.37%. The clinicians included were from 704 hospitals located in 158 cities in China. Among the hospitals, 444 (63.07%) were tertiary hospitals and 465 (66.05%) teaching hospitals. The beds of the hospitals were distributed as follows: <1000, 105/704 (14.91%); 1000–2000, 317/704 (45.03%); and >2000, 282/704 (40.06%). The beds of ICUs were as follows: <10, 84/704 (11.93%); 10–20, 274/704 (38.92%); and >20, 346/704 (49.15%). The ratio of nurses and beds was almost <2.5 (648/704 [92.05%]), and the ratio of doctors and beds was mainly <0.8 (626/704 [88.92%]). The constituent ratios of clinicians from different regions were such that the ratios of the title (senior/junior; senior: above associate senior physician; and junior: attending physician and resident physician) and the ranks of working time (>10 years; 5–10 years; <5 years) of the clinicians in the four regions were the same ($\chi^2 = 7.605$, $P = 0.055$; $\chi^2 = 9.716$, $P = 0.137$, respectively). The ratios of the educational background (graduate/undergraduate; graduates: PhD and postgraduate) of the clinicians in the four regions were different ($\chi^2 = 18.597$, $P < 0.001$) [Table 1]. The main reason for the difference was that the rate of undergraduates in R4 was higher than that in the other regions.

Current practice of pain, agitation, and delirium in Intensive Care Units in China

Of the 766 (75.77%) clinicians assessing pain in daily work, only 463 (45.80%) used pain scores. The top three popular pain scores were the visual analog scale (VAS, 358/772, 46.37%), critical care pain observation tool (CPOT, 173/772, 22.41%), and numerical analog scale (115/772, 14.9%). Most clinicians preferred to use fentanyl (662/1011, 65.48%), sufentanil (530/1011, 52.42%), and morphine (458/1011, 45.3%) for analgesia. Of the 912 (90.21%) clinicians assessing sedation needs in daily work, 697 (68.94%) used sedation scales. The Richmond agitation-sedation scale (RASS, 496/883, 56.17%) and Ramsay scale (335/883, 37.94%) were the most popular scales for sedation. The most popular sedation agents used by the clinicians were midazolam (864/1011, 85.46%), propofol (860/1011, 85.06%), and dexmedetomidine (638/1011, 63.11%). Of the 675 (66.77%) clinicians assessing delirium in daily work, 344 (34.04%) used delirium scales. Most of them used the confusion assessment method for the ICUs (CAM-ICUs, 463/524, 83.51%). Dexmedetomidine (538/1011, 53.21%), haloperidol (438/1011, 43.32%), and midazolam (316/1011,

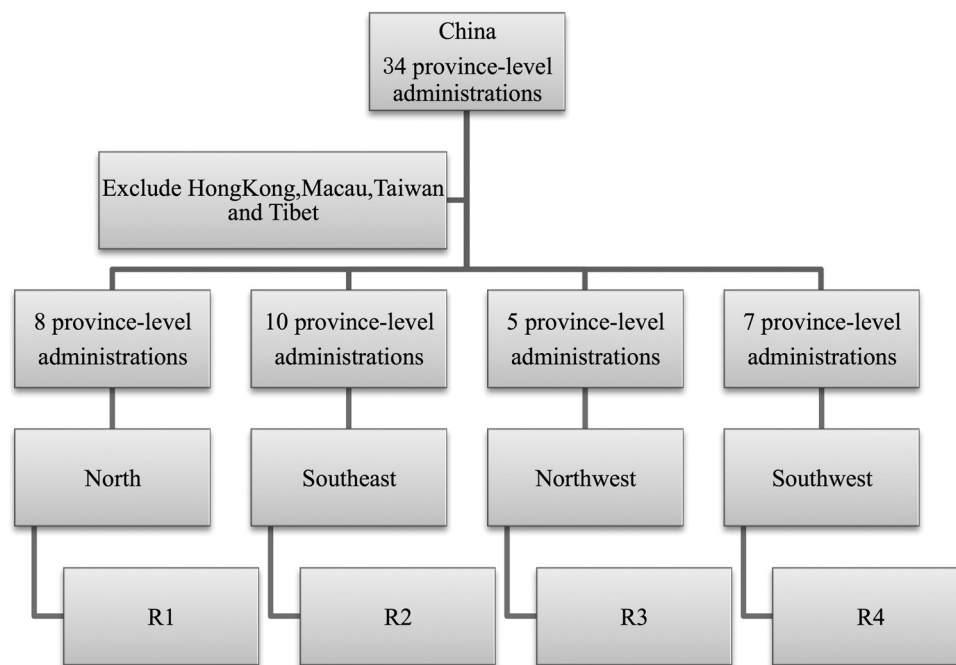


Figure 1: Flowchart of this study. R1, R2, R3, and R4 represent the four regions of China: North, Southeast, Northwest, and Southwest.

Items	R1 (n = 308)	R2 (n = 347)	R3 (n = 137)	R4 (n = 219)	χ^2	P
Titles						
Senior/junior	150/158	136/211	65/72	89/130	7.605	0.055
Educational background						
Postgraduate/undergraduate	168/140*	186/161*	61/76	83/136	18.597	<0.001
Working time (years)						
>10/5–10/<5	92/141/75	86/147/114	41/51/45	65/83/71	9.716	0.137

Data are presented as n. R1, R2, R3, and R4 represent the four regions of China: North, Southeast, Northwest, and Southwest. * $P < 0.001$ compared with R4; $\chi^2_{1,4} = 14.218$, $\chi^2_{2,4} = 13.275$.

31.26%) were the most commonly used agents for delirium treatment.

While choosing analgesics and sedatives, the clinicians put the pharmacological characteristics of the drugs in the first place (668/1011, 66.07%; 772/1011, 76.36%) rather than the adverse effect and the cost of the drugs. Daily interruption for sedation was carried out by 680 (67.26%) clinicians. Most of the clinicians (882/1011, 87.24%) used analgesics while using sedatives. Of the 738 (73%) clinicians titrating the sedatives on the basis of the proposed target sedation level, 268 (26.61%) clinicians just depended on their clinical experience. Nearly more than a half of the clinicians (519/1011, 51.34%) never used other nondrug strategies for PAD. Moreover, the relationship between the categories of clinicians and the PAD practice indicated that the title of clinicians had no association with the practice, but the working time of the clinicians was a significant factor [Table 2].

Comparison of pain, agitation, and delirium practice in the four regions (R1, R2, R3, and R4) of China

The rates of pain assessment from clinicians in the four regions were different ($\chi^2 = 12.699$, $P = 0.005$). The rates of pain assessment in R2, R3, and R4 were the same ($\chi^2 = 0.000$, $P = 1.000$). The rates in R1 was the lowest ($\chi^2_{1-2} = 9.269$, $\chi^2_{1-4} = 7.053$, $P_{1-2} = 0.002$, $P_{1-4} = 0.008$). The rates of pain score used in the four regions were also different ($\chi^2 = 8.541$, $P = 0.036$). The rate of application of pain score in R4 was the highest, followed by R2, R3, and R1. However, only the comparison between R4 and R1 was statistically significant ($\chi^2 = 7.294$, $P_{1-4} = 0.007$).

The rates of sedation assessment in the four regions were the same ($\chi^2 = 4.754$, $P = 0.191$), but the sedation scores were different ($\chi^2 = 9.313$, $P = 0.025$). The highest was R4, and the lowest was R1 ($\chi^2 = 8.679$, $P_{1-4} = 0.003$). The rates of delirium assessments and scores were the same in the four regions ($\chi^2 = 3.630$ and 0.750 , $P = 0.304$ and 0.861 , respectively) [Table 3].

The first choices of scores of PAD in the four regions were the same: VAS for pain assessment, RASS for sedation assessment, and CAM-ICU for delirium assessment. The rates of VAS in the four regions were different ($\chi^2 = 16.661$, $P = 0.001$), but the rates of RASS and CAM-ICU were the same in the four regions ($\chi^2 = 7.118$ and 0.238 , $P = 0.068$ and 0.971 , respectively) [Table 4]. The choices of the top three PAD drugs in the four regions seemed a little different [Table 5]. Fentanyl was the most popular analgesic in the four regions of China. Sufentanil was used in R2, R3, and R4 rather than in R1 for the top three. Dezocine was more popular in R1 and R2 than in R3 and R4. For the sedatives, the most popular drugs were midazolam, propofol, and dexmedetomidine in the four regions. The sequence of the sedatives in the four regions was a little different. The clinicians in R1 and R2 preferred midazolam to propofol, but the clinicians in R3 and R4 preferred propofol to midazolam. The first choice for clinicians to treat delirium was dexmedetomidine in R1 and R2 but haloperidol in R3 and R4. Comparing midazolam and propofol, atypical antipsychotics was more popular in R4 than that in the other regions for delirium treatment.

Table 2: Relationship between classification of clinicians and practice of PAD

Items	Titles		χ^2	P	Education background		χ^2	P
	Senior (n = 440)	Junior (n = 571)			PG (n = 498)	UG (n = 513)		
Pain assessment	327 (74.3)	439 (76.9)	0.756	0.385	383 (76.9)	383 (74.7)	0.579	0.447
Pain score	217 (49.3)	246 (43.1)	3.646	0.056	240 (48.2)	223 (43.5)	2.084	0.149
Sedation assessment	398 (90.5)	514 (90.0)	0.016	0.900	465 (93.4)	456 (88.9)	1.759	0.185
Sedation score	316 (71.8)	381 (66.7)	2.777	0.096	356 (71.5)	341 (66.5)	2.738	0.098
Daily interruption	282 (64.1)	398 (69.7)	3.303	0.069	315 (63.3)	365 (71.2) [†]	6.802	0.009
AFS	376 (85.5)	506 (88.6)	1.957	0.162	436 (87.6)	446 (86.9)	0.039	0.844
Delirium assessment	289 (65.7)	386 (67.6)	0.330	0.565	336 (67.5)	339 (66.1)	0.161	0.688
Delirium score	155 (35.2)	189 (33.1)	0.411	0.522	201 (40.4)	143 (27.9) [†]	16.998	<0.001
Nondrug strategies	220 (50.0)	299 (52.4)	0.465	0.495	237 (47.6)	282 (55.0)	5.218	0.022

Items	Working time (years)			χ^2	P
	>10 (n = 282)	5–10 (n = 422)	<5 (n = 305)		
Pain assessment	230 (81.0)*	316 (74.9)	220 (72.1)	6.589	0.037
Pain score	152 (53.5)*	178 (42.2)	223 (73.1)	9.639	0.008
Sedation assessment	268 (94.4)*	382 (90.5)	262 (85.9)	12.009	0.002
Sedation score	221 (77.8)*	278 (65.9)	198 (64.9)	14.605	0.001
Daily interruption	187 (65.8)	283 (67.1)	210 (49.8)	0.617	0.735
AFS	264 (93.0)*	368 (87.2)	250 (82.0)	16.618	<0.001
Delirium assessment	197 (69.4)	290 (68.7)	188 (61.6)	5.204	0.074
Delirium score	104 (36.6)	135 (32.0)	105 (34.4)	1.652	0.438
Nondrug strategies	135 (47.5)	222 (52.6)	162 (53.1)	2.301	0.316

Data are presented as n (%). * $P < 0.01$, compared with 5–10 working years and <5 working years; [†] $P < 0.05$, compared with postgraduate. PAD: Pain, agitation and delirium; AFS: Analgesia first sedation; PG: Postgraduate; UG: Undergraduate.

DISCUSSION

Most of the questions in the questionnaire were designed with three choices, considering the psychological status of the respondents: “yes, no, and sometimes yes.” However, all the answers of “sometimes yes” to the question “Do you assess pain?” were combined with the answer “no” when the data were analyzed. That means, the rate of pain assessment was the lowest and a more realistic result, and so were the other answers. Looking back at the previous surveys, the rates of clinician’s concept on sedation were on the rise, the rates of assessment tools were also increasing, but the rate of actual daily practice was still the same (about 78%). Because it is not easy to give the ICU patients optimal PAD care as it is very complicated, careful monitoring, change in the treatment plan time to time, and cooperation with other colleagues are needed. However, the present survey showed a satisfactory application status of the practice of PAD in China. First, more than 90% clinicians assessed the sedation needs and nearly 70% of them used sedation scales, which was even better than that in some developed countries. It is generally accepted that assessment and using assessment tools are the first important steps of PAD management. Every patient should receive adequate pain control.^[22] Therefore, the use of pain

scores needs to be improved in China, as only less than half clinicians used them.

The second significant finding was that in China, the common choices of PAD scores and agents were in accordance with the guidelines and present evidence-based studies. In other words, the application of PAD guideline was accepted by Chinese clinicians in the ICUs to a large extent. For instance, the most common pain and sedation scores were VAS for verbal patients and CPOT for nonverbal patients, and RASS and Ramsay for sedation. The most common agents for analgesic were still opioids, such as fentanyl and sufentanil. However, the popular agents for sedation were midazolam, propofol, and dexmedetomidine. The rates of use of propofol and dexmedetomidine significantly increased than in prior surveys.^[15,19] The variation tendency also indicated that the status of nonbenzodiazepines in comparison with benzodiazepines was much better.^[23-26] Dexmedetomidine was regarded as the most common sedative by more than 60% clinicians. All of these findings confirmed that the development of PAD practice in China follows the international guidelines.

The occurrence of delirium increasingly catches clinicians’ attention because delirium can cause big harm to patients

Table 3: PAD assessment and scales in the four regions of China

Items	R1 (n = 308)	R2 (n = 347)	R3 (n = 137)	R4 (n = 219)	χ^2	P
Pain assessment	208 (67.35)	271 (78.10)*	107 (78.10)	171 (78.08)*	12.699	0.005
Pain score	121 (39.29)	167 (48.13)	63 (45.99)	112 (51.14)†	8.541	0.036
Sedation assessment	277 (89.94)	305 (87.90)	126 (91.98)	204 (93.15)	4.754	0.191
Sedation score	201 (65.26)	234 (67.44)	93 (67.88)	169 (77.17)‡	9.313	0.025
Delirium assessment	206 (66.88)	238 (68.59)	82 (59.85)	149 (68.04)	3.630	0.304
Delirium score	100 (32.47)	118 (34.01)	50 (36.50)	76 (34.70)	0.750	0.861

Data are presented as n (%). R1, R2, R3, and R4 represent the four regions of China: North, Southeast, Northwest, and Southwest. * $P < 0.01$, compared with R1 ($\chi^2_{1-2} = 9.269$, $\chi^2_{1-4} = 7.053$); † $P < 0.01$, compared with R1 ($\chi^2_{1-4} = 7.294$); ‡ $P < 0.01$, compared with R1 ($\chi^2_{1-4} = 8.679$). PAD: Pain, agitation, and delirium.

Table 4: Percentage of the first choice of PAD scores in the four regions of China

Items	R1	R2	R3	R4	χ^2	P
Pain score	121/211 (57.35)	108/278 (38.85)*	47/105 (44.76)	82/178 (46.07)	16.661	0.001
Sedation score	129/258 (50.00)	184/302 (60.92)	71/121 (58.68)	112/202 (55.45)	7.118	0.068
Delirium score	138/157 (87.90)	159/181 (87.85)	69/77 (89.61)	97/109 (88.99)	0.238	0.971

Data are presented as n/N (%). * $P < 0.001$, compared with R1 ($\chi^2_{1-2} = 16.483$). R1, R2, R3, and R4 represent the four regions of China: North, Southeast, Northwest, and Southwest. PAD: Pain, agitation, and delirium.

Table 5: Top three choices of agents in PAD treatment in the four regions of China

Items	R1 (n = 308)	R2 (n = 347)	R3 (n = 137)	R4 (n = 219)
Analgesic	Fen > mor > dez	Fen > suf > mor	Fen = suf > mor	Fen > suf > mor
	64.29>52.92>38.31	64.55>59.65>44.38	58.39 = 58.39>37.96	73.06>62.10>46.12
Sedatives	Mid > pro > dex	Mid > pro > dex	Pro > mid > dex	Pro > mid > dex
	87.34>81.17>69.16	87.03>84.15>62.82	93.43>79.56>47.45	86.76>84.02>64.84
DDR	Dex > mid > hal	Dex > hal > mid	Hal > dex > pro	Hal > dex > aa
	62.66>38.31>31.17	53.89>39.19>32.56	52.28>34.31>31.39	60.73>50.68>22.37

Data are presented as %. PAD: Pain, agitation, and delirium; aa: Atypical antipsychotics; DDR: Delirium drug resistance; dex: Dexmedetomidine; dez: Dezocine; fen: Fentanyl; hal: Haloperidol; mid: Midazolam; mor: Morphine; pro: Propofol; suf: Sufentanil.

physically and mentally and have a negative impact on the prognosis.^[27,28] The rates of delirium assessment were always at a low level because of no satisfactory assessment tools for application. The situation in China was also the same compared with other countries. It is hoped that more objective assessment tools or parameters in the future can resolve the issue.^[29] Studies on delirium^[30-34] indicate that the first choice of drugs for delirium resistance has changed from haloperidol to dexmedetomidine,^[35] consistent with the present survey.

In addition to drug treatment, a lot of strategies exist to manage PAD. In the present study, nearly half of the clinicians applied some nondrug strategies in their work. The most popular strategies were to give patients psychological comfort by communicating or allowing their family members to give the company, playing music, and moving them as soon as possible. However, further researches are needed to support the evidence regarding which strategy is more effective. The clinicians can explore some useful and feasible strategies for Chinese patients.

The characteristics of clinicians showed that the working time was an important factor pertaining to the analgesic and sedation practice of clinicians rather than the title and the educational background. The main reason might be that most of the PAD practice was for the intensive illness patients living in an ICU settlement. The longer one worked in other departments, the higher the title one got; however, this did not guarantee more experience in pain and sedation assessment. The longer one worked in the ICUs; the better-experienced one might be in pain control and sedation treatment.

PAD practices vary nationally and internationally for the different background of medical resource and study development. Although the PAD guideline might pose lots of problems, it is quite important to clinical practice.^[36] If the guideline can accord with the country's actual status, the efficacy of the management will be prominent. In addition to the United States, for instance, Germany investigated and monitored its sedation practice year by year.^[16-18] Moreover, on the basis of the surveys, Germany explored its own sedation guideline and updated it.^[14,37] All these efforts effectively improved the analgesia, sedation, and delirium treatment in ICUs in Germany. As a great developing country, China has a vast territory. The PAD practice in the different regions of China offers important information. The comparisons of the four regions showed that the pain and sedation assessments in R1 needed more attention. However, the reason for this result was not clear.

This study was a survey in the form of a questionnaire that relied on the perceptions and recall of clinicians. It did not reflect the actual events in the clinical situation. The actual events from patients seemed worse than the perceptions from clinicians. Thus, this survey had some limitations in judging whether the patients got appropriate management. However, this nationwide survey was the first-hand information on PAD practice in China, which objectively reflected the

progress and problems in the practice of PAD. Moreover, the included ICUs of the study showed that the ratios of staff and beds were much lower than needed in most of the hospitals in China. However, PAD assessment and management is works that need the cooperation of enough staff. Therefore, the lack of medical supply from staff might be the main obstacles to PAD practice in China.

In conclusion, the practice of PAD assessment and management in China was in accordance with the international situations. The guideline and the updated recommendations were accepted by most of the clinicians in China. The pain assessment and control were the basic treatment in the process of sedation and delirium management, and therefore, they should be emphasized in the future working in China. It is hoped that more effective and feasible nondrug strategies can be applied in the PAD management. Comparing the four regions of China showed that PAD practice across China is a little different; however, the trend was consistent.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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