The preventive effect of dexmedetomidine on paroxysmal sympathetic hyperactivity in severe traumatic brain injury patients who have undergone surgery: a retrospective study

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Abstract

16 **Background.** Paroxysmal sympathetic hyperactivity (PSH) results and aggravates in secondary brain injury, which

17 seriously affects the prognosis of severe traumatic brain injury patients. Although several studies have focused on

18 the treatment of PSH, few have concentrated on its prevention.

19 **Methods.** Ninety post-operation (post-op) severe traumatic brain injury (sTBI) patients admitted from October 2014

20 to April 2016 were chosen to participate in this study. Fifty of the post-op sTBI patients were sedated with

21 dexmedetomidine and were referred to as the "dexmedetomidine group" (admitted from May 2015 to April 2016).

22 The other 40 patients (admitted from October 2014 to May 2015) received other sedations and were referred to as

23 the "control group." The two groups were then compared based on their PSH scores and the scores and ratios of

24 those patients who met the criteria of "probable", "possible" and "unlikely" using the PSH assessment measure

25 (PSH-AM) designed by Baguley et al. (2014). The durations of the neurosurgery intensive care unit (NICU) and

26 hospital stays and the Glasgow outcome scale (GOS) values for the two groups were also compared to evaluate the

27 therapeutic effects and the patients' prognosis.

28 **Results.** The overall PSH score for the dexmedetomidine group was 5.26±4.66, compared with 8.58±8.09 for the

29 control group. The difference between the two groups' PSH scores was significant (P = 0.017). The score of the

30   patients who met the criterion of "probable" was 18.33±1.53 in the dexmedetomidine group and 22.63±2.97 in the

31   control group, and the difference was statistically significant (P = 0.045). The ratio of patients who were classified

32   as "unlikely" between the two groups was statistically significant (P = 0.028); that is, 42 (84%) in the

33   dexmedetomidine group and 25 (62.5%) in the control group. The differences in NICU, hospital stays and GOS

34   values between the two groups were not significant.

35   **Conclusion.** Dexmedetomidine has a preventive effect on PSH in sTBI patients who have undergone surgery.

36   # Introduction

37   Sympathetic activity after stress is the body's necessary protective response, but sympathetic overactivity

38   following acute brain injury fosters hemodynamic instability and contributes to secondary brain damage, which

39   severely affects the prognosis (Baguley et al. 2006; Hinson & Sheth 2012; Lv et al. 2011). Paroxysmal sympathetic

40   hyperactivity (PSH) is a syndrome characterized by paroxysmal episodes of sympathetic surges that can manifest as

41   hyperthermia, diaphoresis, tachycardia, hypertension, tachypnea, and dystonic posturing (Baguley et al. 2014). Since

42   Wilder Penfield's first report on the syndrome, numerous terms have been used to describe it, including diencephalic

43   autonomic epilepsy, dysautonomia, paroxysmal autonomic instability with dystonia, and PSH (Penfield 1929;

44   Perkes et al. 2011). It has been reported that 7.7~33% of traumatic brain injury patients in intensive care units (ICUs)

45   suffer from this disorder (Baguley et al. 2007b; Dolce et al. 2008; Fearnside et al. 1993; Fernandez-Ortega et al.

46   2012; Fernandez-Ortega et al. 2006; Hendricks et al. 2007; Lv et al. 2010; Lv et al. 2011; Perkes et al. 2010; Perkes

47   et al. 2011; Rabinstein 2007).

48   PSH episodes can last for several minutes to hours and may recur multiple times during the day (Blackman et al.

49   2004). Unstable conditions such as high blood pressure or fever, can result in and aggravate secondary brain injury,

50   which is considered to be one of the main causes of unfavorable prognosis (Baguley 2008a; Baguley et al. 2007a;

51   Fernandez-Ortega et al. 2012; Fernandez-Ortega et al. 2006; Greer et al. 2008). PSH can also cause a

52   hypermetabolic state, unopposed inflammation, and weight loss—all of which can lead to worse outcomes and

53   prolonged hospital stays (Choi et al. 2013; Mehta et al. 2008; Tracey 2007). Several studies have focused on how to

54   treat PSH, but few have concentrated on its prevention.

55   Dexmedetomidine is a new selective alpha-2 agonist that has been shown to decrease sympathetic activation,

56   with the effect on sedation, analgesia, and antianxiety without significant inhibition of respiration (Martin et al. 2003;

57   Panzer et al. 2011; Venn et al. 2000). It has been formally approved by the Food and Drug Administration of the

58   United States of America (FDA) for use in sedating ICU patients since 1999. The Department of Neurosurgery at

59   Ren Ji Hospital introduced dexmedetomidine for the routine postoperative sedation of sTBI patients in May 2015. In

60   this article, we report that dexmedetomidine may have a preventive effect on PSH in postoperative patients who

61   have suffered severe traumatic brain injury.

62   **Methods**

63   **Study population**

64   Retrospectively and consecutively, all of the patients included in this study were admitted to the Department of

65   Neurosurgery at Ren Ji Hospital from October 2014 to April 2016. Consecutive patients were included if they were

66   older than 18, had suffered sTBI, and had undergone an operation. Patients were excluded if they met any of the

67   following criteria: serious hepatic dysfunction (Child-Pugh class B or C); serious renal dysfunction (undergoing

68   dialysis before surgery; or serum creatinine > 445 μmol/L and/or blood urea nitrogen > 20 mmol/L in preoperative

69   laboratory examination); unstable haemodynamics at NICU admission, such as bradycardia and hypotension; death

70   occurring within 24 h after surgery. Of the 103 consecutively recorded patients, 13 were excluded based on the

71   preceding criteria. Based on the post-op sedation received, the remaining 90 patients were divided into two groups:

72   the control group (admitted from October 2014 to May 2015) and the dexmedetomidine group (admitted from May

73   2015 to April 2016). This study was approved by the Ethics Committee of Ren Ji Hospital (Ethical Application Ref:

74   [2016]W018).

75   **Treatment protocol**

76   For the dexmedetomidine group, when each patient was placed in the NICU after his or her operation,

77   dexmedetomidine was administrated at an initial loading dose of 0.8 μg/kg within 10 minutes, followed by a

78   continuous infusion at 0.25~0.75 μg/(kg · h)$^{-1}$. For the control group, propofol or midazolam was administered by

79   intravenous pump infusion. Propofol was initiated at 2 mg/(kg · h)$^{-1}$ and midazolam was initiated at 0.1 mg/(kg ·

80   h)$^{-1}$. Diazepam is added at the discretion of doctors as a component of a goal-directed sedation regimen. All of the

81   patients were maintained at a Riker sedation-agitation scale (SAS) of 3 to 4 and the sedations were withdrawn

82   gradually starting on day 5, depending on the patient's condition. Upon the onset of PSH symptoms, symptomatic

83   treatments such as cooling the temperature and lowering the heart rate were administrated as soon as possible.

84   Verbal informed consent was obtained from patients' decision makers.

85   **Data collection and outcome assessment**

86   In the NICU, on an hourly basis, the nurses recorded each patient's heart rate, respiratory rate, systolic blood

87   pressure, temperature, sweating, and posture during episodes. Once the patients were transferred to ordinary wards,

88   abnormal signs and symptoms of PSH were observed by trained nurses and events were reported to the doctors in

89   charge of the patients and recorded. The patients were scored using the PSH Assessment Measure (PSH-AM)

90   developed by Baguley et al. (2014). The PSH-AM is designed to have two components-- one addressing the

91   probability of the diagnosis (the Diagnosis Likelihood Tool [DLT]) and another assessing the severity of the clinical

92   features (the Clinical Feature Scale [CFS]). The numerical output of these two components are added together to

93   estimate the diagnostic likelihood of PSH. Regarding the probability of a PSH diagnosis, a score of less than 8

94   indicated "unlikely," a score from 8 to 16 indicated "possible," and a score greater than or equal to 17 indicated

95   "probable" (Baguley et al. 2014).

96   All patients received a three-month follow-up evaluation by telephone. The outcomes were quantified using the

97   Glasgow Outcome Scale (GOS)(Jennett & Bond 1975) at discharge and after three months. The GOS were

98   evaluated based on the descriptions provided by the patients' relatives three months after injury to evaluate the

99   prognosis. The lengths of the patients' NICU and hospital stays were also collected to assess the therapeutic effects.

100 **Statistical analysis**

101   A statistical analysis was performed using SPSS Version 20.0.0 (SPSS Inc, Chicago, Illinois). The continuous

102 variables were presented as mean ± standard deviation (SD) and the proportions were calculated for the categorical

103   variables. For the continuous variables, group comparisons were made using parametric t-tests if the data followed

104   normal distribution. Otherwise, non-parametric Mann–Whitney-U tests were used. For the categorical variables,

105   such as gender, diagnosis and surgery type, group comparisons were made using a chi-quadrat test or a Fisher's

106   exact test if at least one value was <5. Significance was set at p<0.05. To assess the power of our study, we

107   conducted power calculations by using G*power (Faul et al. 2007).

108   **Results**

109   The data entry was completed in July 2016, when all of the patients had received their three-month follow-up.

110   The patients' data were collected for retrospective analysis. No significant differences were noted between the two

111   groups in relation to age, gender, pre-operative GCS, diagnosis, time from injury to surgery, and type of surgery.

112   The demographic patient data are listed in Table 1.

113   The patients in the dexmedetomidine group were sedated for a period of 5.46±2.82 days, compared with

114   6.08±2.95 in the control group (p = 0.317). The total dose of dexmedetomidine given to each person was 4.79±2.47

115   mg. Dexmedetomidine was not administrated to the patients in the control group. The PSH-AM score of the patients

116   in the dexmedetomidine group was significantly lower than that of those in the control group (5.26±4.66 vs.

117   8.58±8.09, P = 0.017).

118   No significant differences were noted between the two groups regarding the ratio of patients who met the

119   criteria of "probable" (three (6%) in the dexmedetomidine group vs. eight (12.5%) in the control group, P = 0.056)

120   and "unlikely" (3.67±2.40 in the dexmedetomidine group vs. 3.28±2.30 in the control group, P = 0.519). However,

121   the score of patients who met the "probable" criterion in the dexmedetomidine group was 18.33±1.53, compared

122   with 22.63±2.97 in the control group (P = 0.045). Moreover, 42 (84%) of the patients in the dexmedetomidine group

123   met the "unlikely" criterion, compared with 25 (62.5%) patients in the control group (P = 0.028). No significant

124   differences in the groups were established for patients who met the "possible" criterion, in number or score (Figures

125   1 and 2).

126   In NICU, the two groups had the same mortality of 20% (10 of 50 in the dexmedetomidine group and 8 of 40 in

127   the control group). No more patients died after transfered to ordinary wards. The patients in the dexmedetomidine

128   group stayed in the NICU for an average duration of 15.70±13.07 days and in the hospital for 23.50±16.58 days,

129   compared with 20.65±16.74 and 28.53±20.28 days, respectively, in the control group (P = 0.119 and P = 0.174)

130   (Figure 3). The GOS value at discharge was 3.00±1.28 in the dexmedetomidine group, compared with 2.75±1.15 in

131   the control group (P = 0.338). The GOS vaule three months after sTBI in the dexmedetomidine group was 3.42±1.47,

132   compared with 3.05±1.43 in the control group (P = 0.234) (Figure 4, Table 1). The statistical power for the outcome

133   measures described above is relatively low (21%-42%).

Discussion

135   Severe traumatic brain injury, which is associated with considerable mortality and morbidity, represents a

136   significant public health problem around the world. PSH after sTBI is one of the important factors contributing to

137   adverse outcomes. The first diagnostic criteria for PSH were published in 1993 (Fearnside et al. 1993). Since that

138   time, different criteria have been proposed mainly due to the presence of the following signs and symptoms in the

139   absence of other potential causes: fever, tachycardia, hypertension, tachypnea, excessive diaphoresis and extensor

140   posturing, or severe dystonia (Baguley et al. 2014; Blackman et al. 2004; Dolce et al. 2008; Perkes et al. 2011;

141   Rabinstein 2007). A PSH diagnosis is one of exclusion. Considering differential diagnoses such as sepsis, systemic

142   inflammatory response syndrom, or sedation withdrawal is crucial, but sometimes difficult. Baguley et al. (2014)

143   proposed a consensus of diagnostic criteria for PSH—specifically, a probabilistic system that assigned a diagnostic

144   likelihood rather than providing a definitive diagnosis (Baguley et al. 2014). This diagnostic system enables medical

145   workers to diagnose PSH more precisely and provides a quantization foundation for PSH evaluation.

146   The pathophysiology of PSH is unclear, and related theories have not been empirically tested. Initially, the

147   cause of the condition was thought to be diencephalic discharges (Bhigjee et al. 1985; Penfield 1929). However,

148   later studies identified no seizure activities in PSH using electroencephalography (Baguley et al. 2006; Boeve et al.

149   1998). The current consensus is that epilepsy is not the cause of PSH (Bullard 1987; Pranzatelli et al. 1991; Thorley

150   et al. 2001). The accepted model is the excitatory–inhibitory ratio (EIR) model (Baguley 2008b), which proposes

151   that the afferent stimulus is normally controlled by tonic inhibitory drive from diencephalic centers. Once the tonic

152   inhibition cycle is broken, there is a positive-feedback loop that produces sympathetic over-activity following any

153   afferent stimuli (Baguley et al. 2009a; Baguley et al. 2009b). This model explains how a normally non-noxious

154   stimulus can cause an uncontrolled sympathetic response.

155   For PSH, timely diagnosis, swift episode control, and reduced onset frequency are all crucial in improving

156   prognosis. Regarding the treatment of PSH, beta-blockers, which attenuate sympathetic activation, are now widely

157   used to control its onset (Do et al. 2000; Rabinstein & Benarroch 2008; Sneed 1995). Morphine, a potent μ-opioid

158   receptor agonist; Bromocriptine, a dopamine receptor agonist; and baclofen, a GABA receptor agonist, have also

159   been reported to successfully alleviate PSH episodes (Becker et al. 2000; Cuny et al. 2001; Ko et al. 2010; Russo &

160   O'Flaherty 2000). However, as few cohort studies guiding PSH treatment exist and the underlying pathophysiology

161   remains unclear, treatment strategies frequently focus on controlling symptoms. For instance, antipyretics are

162   administered to treat hyperthermia, sedatives for agitation, and antihypertensive medications for hypertension (Choi

163   et al. 2013).

164   Dexmedetomidine is a highly selective presynaptic α-2 adrenergic agonist that may block norepinephrine

165   release and enhance sympathetic inhibition to maintain the balance of the unregulated sympathetic feedback loop.

166   Two cases of dexmedetomidine being used to diminish PSH symptoms have been reported (Goddeau et al. 2007;

167   Kern et al. 2016), which may support the disconnection theory. Unlike a traditional sedative such as propofol, which

168   acts on GABA receptors in the cortex, dexmedetomidine displays the actions of analgesia, sedation, and anxiety

169   treatment by acting on the α2 adrenergic receptors in the locus coeruleus (LC) (Nelson et al. 2003). Patients sedated

170   using dexmedetomidine can be awakened at any time to judge changes in their conscious state. It has also been

171   reported that dexmedetomidine has a neuroprotective effect because it inhibits the apoptosis of nerve cells,

172   protecting against local ischemia and slowing the progression of infarction (Cai et al. 2014; Cosar et al. 2009;

173   Dahmani et al. 2005). These features make dexmedetomidine a commonly prescribed sedative in NICUs.

174   PSH prevention to decrease the number and severity of episodes has more significance in improving the

175   outcome of sTBI, compared with the elimination of PSH episodes. Although several studies have focused on

176   treating PSH, few have addressed its prevention. Thus, based on the routine use of dexmedetomidine for post-op

177   sedation and data collected from patients, this study explored whether dexmedetomidine, which is reported to

178   successfully eliminate PSH episodes, also has a preventive effect on this syndrome.

179   We compared the overall PSH-AM scores between the two groups and found that the score for the

180   dexmedetomidine group was significantly lower than that for the control group, indicating that the patients in the

181   dexmedetomidine group had a lower probability of PSH diagnosis. Compared with the control group, the

182   dexmedetomidine group had a lower score of patients meeting the "probable" criterion and a larger ratio of patients

183   meeting the "unlikely" criterion, with a statistically significant difference. The preceding results showed that

184   dexmedetomidine, to some extent, prevented the patients in the dexmedetomidine group from the onset of PSH.

185   The differences in duration of the NICU and hospital stays and in the GOS values at three-month follow-up

186   between the two groups did not reach statistical significance. sTBI is a heterogeneous disease and patients' post-op

187   conditions are variable and protean. Many factors may contribute to an sTBI prognosis. Moreover, the statistical

188   power for the above three outcome measures is relatively low (21%-42%), which may be due to the small sample

189   size. The low statistical power indicates low ability to distinguish the effect from random chance. This may be why

190   our study did not reach a statistically significant difference for these three outcome measures.

191   The onset of PSH is often sudden and short in duration. In addition, the symptoms are often atypical and

192   changeful, which can make a timely diagnosis difficult. Delayed diagnoses and treatment difficulties can result in

193   prolonged NICU and hospital stays, higher medical costs, and poorer outcomes (Hinson & Sheth 2012; Lv et al.

194   2011). Dexmedetomidine is a commonly used sedative in the NICU, and had a preventive effect on post-op PSH in

195   patients with sTBI who have undergone surgery in our study, although the exact mechanism remains unclear. This

196   feature makes it a promising medication for the sedation of post-op sTBI patients and for preventing PSH onset,

197   both of which are significant in reducing postoperative complications, cutting down the duration of hospitalization,

198   and improving prognosis.

199   This study had several limitations. First, it was a single-center study, and thus the findings may not be

200   generalizable to other centers. The two groups were studied over different periods, during which there might have

201   been differences aside from the sedative used after surgery which were failed to recognize. Second, only those sTBI

202   patients who underwent surgery were studied, and therefore these findings may not be generalizable to those who

203   have not undergone surgery. Third, we observed only PSH episodes during hospital stays without long-term follow-

204   up after discharge. Fourth, limited by objective conditions, we evaluated GOS after three months based on the

205   descriptions provided by the patients' relatives or health care givers, which might cause bias. And last, the statistical

206   power for this study is relatively low (21%-42%), which indicates low ability to distinguish the differences. The

207   preceding limitations impair, to some extent, the trustworthiness of our conclusions.

Conclusions

209   This study showed that dexmedetomidine had a preventive effect on PSH in patients with sTBI who have

210   undergone surgery. The effect was detected as compared to other sedation regimes (midazolam, propofol, and

211   diazepam) with limited statistical power. To our knowledge, no randomized controlled trial to date has studied the

212   preventive effect of dexmedetomidine on PSH for paients with sTBI. This must be confirmed by additional high-

213   level, evidence-based medical research.

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Figure 1

Ratio of patients meeting different criteria regarding likelihood of PSH diagnosis

The ratio of patients who meet the criteria of "probable", "possible", and "unlikely" respectively, in the dexmedetomidine group and in the control group. * indicates significance (p=0.028).

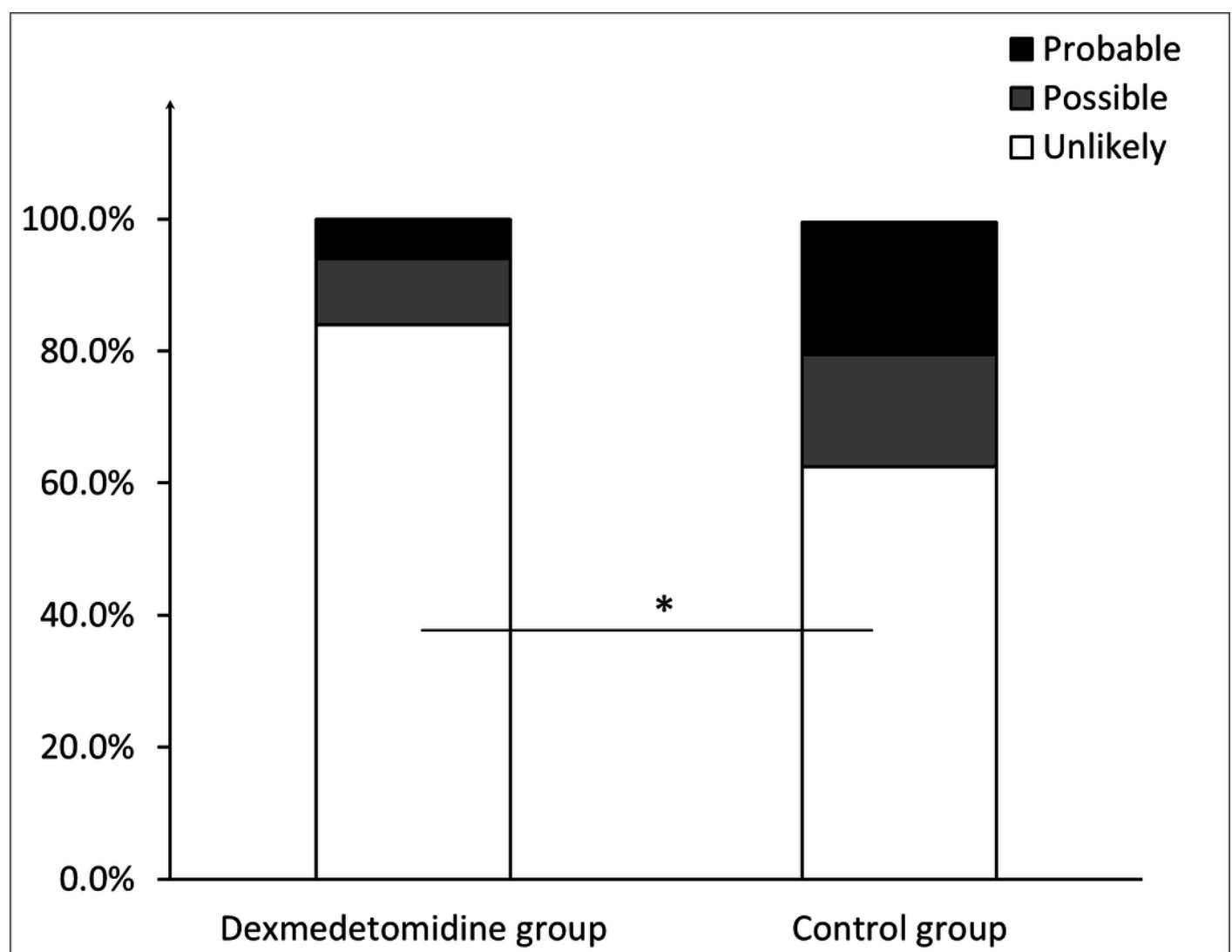



Figure 2

Scores of patients meeting different criteria regarding likelihood of PSH diagnosis

The comparison of the PSH scores of the patients who meet the criteria of "probable", "possible", and "unlikely", respectively, between the dexmedetomidine group and the control group. * indicates significance (p=0.045).

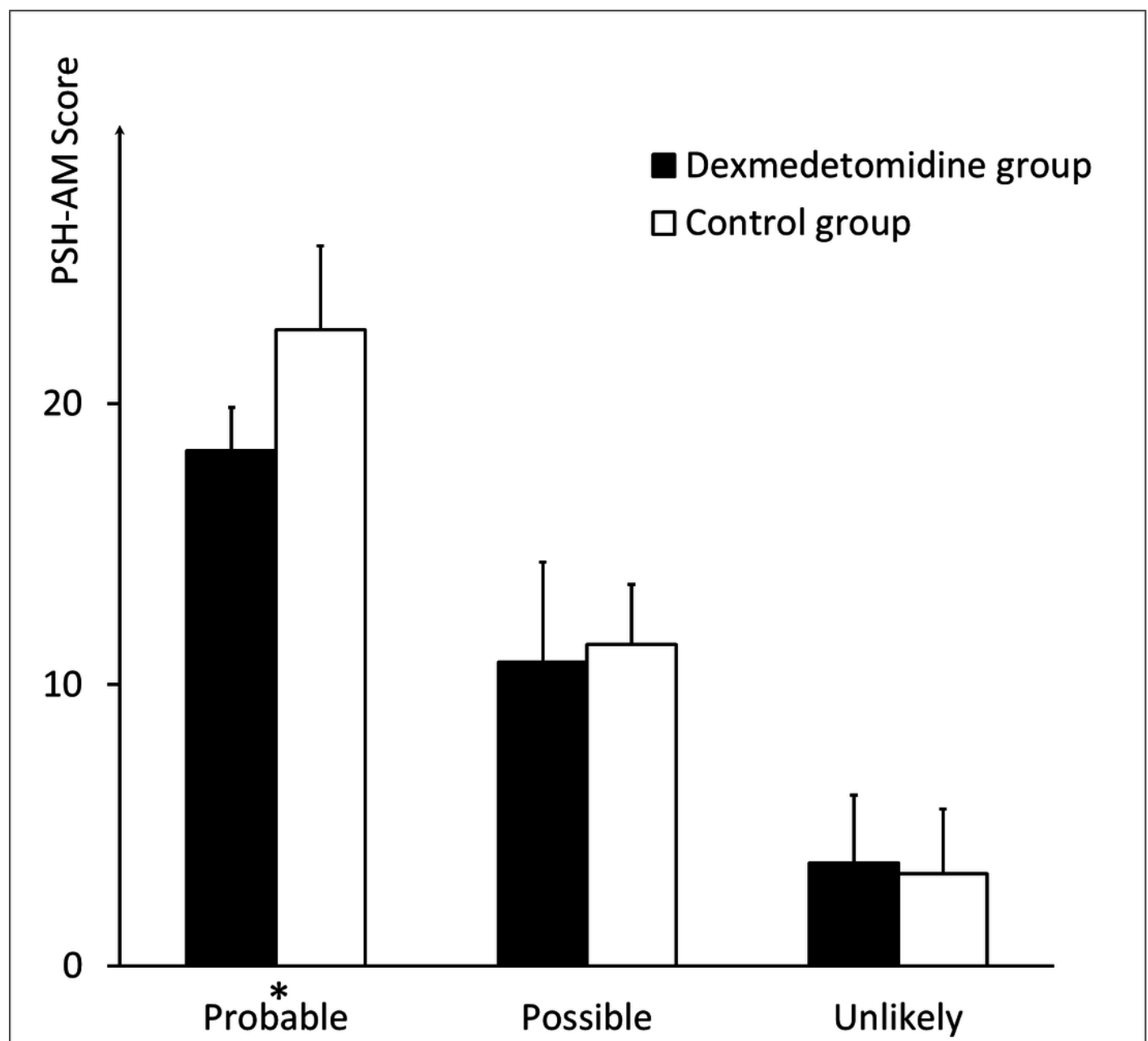



Figure 3

NICU and hospital stay of the two groups

The comparison of the duration of the NICU and hospital stays between the dexmedetomidine group and the control group.

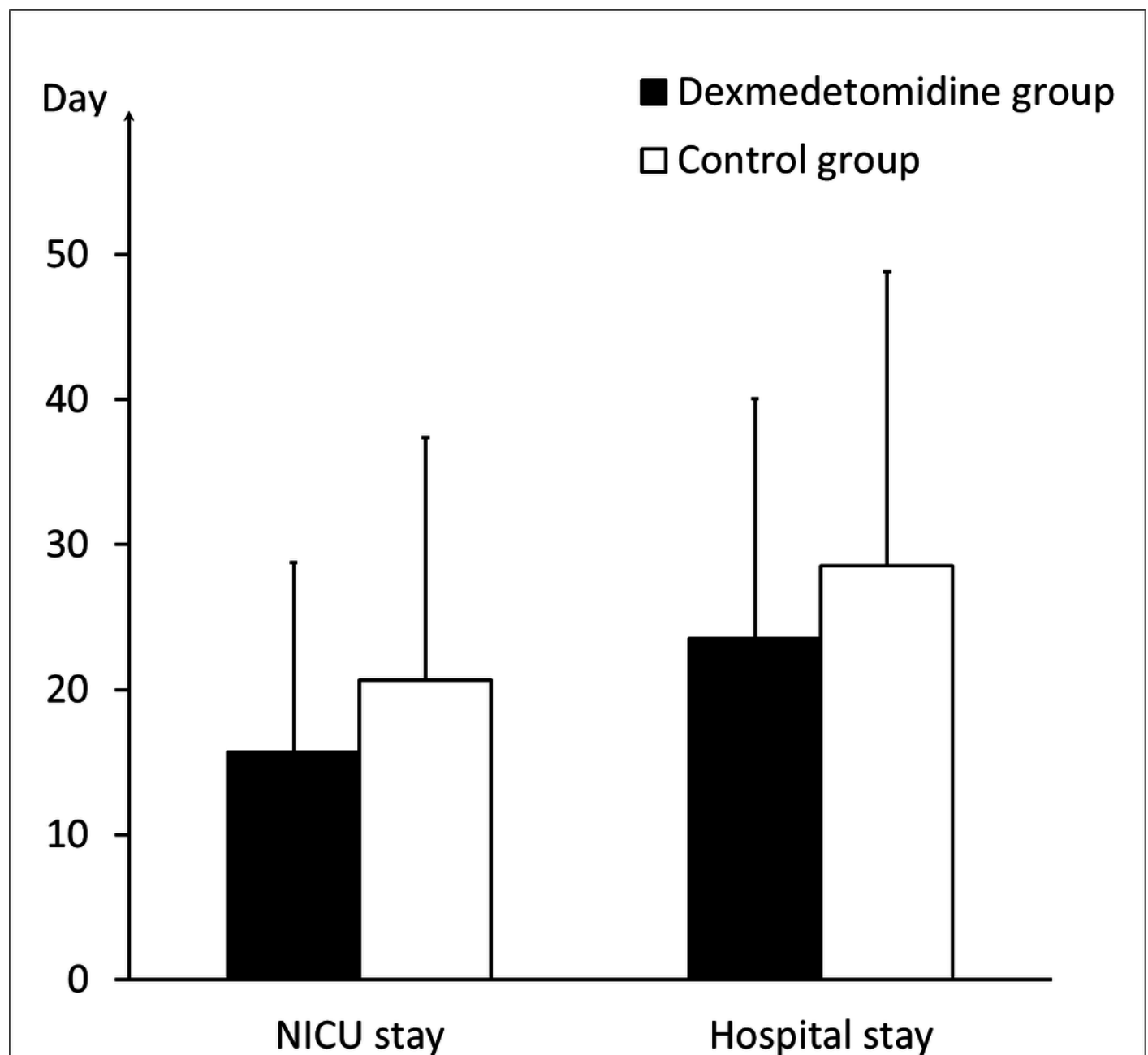
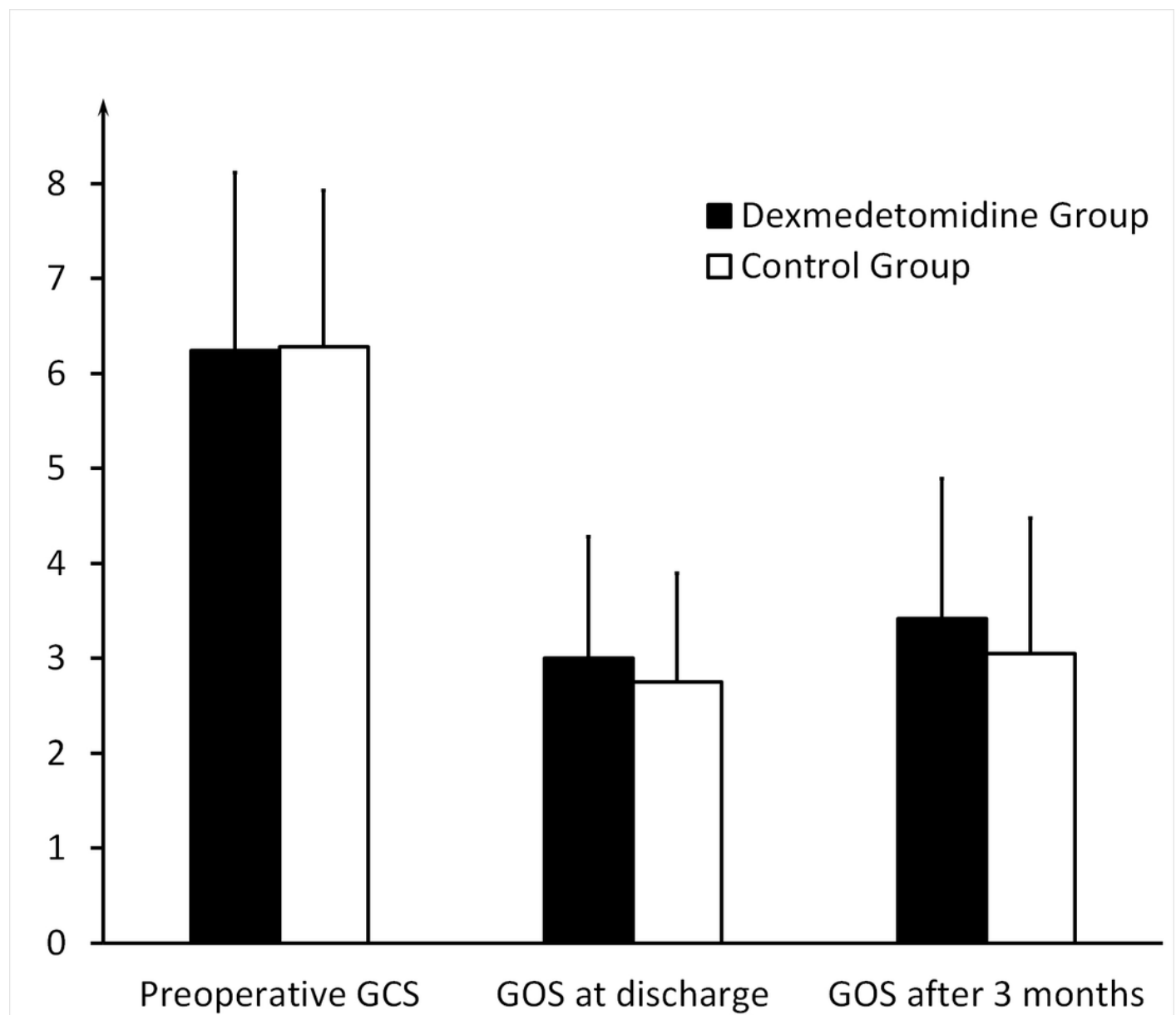



Figure 4

Outcome of the two groups

The preoperative GCS, GOS at discharge, and GOS after three months in the
dexmedetomidine group and the control group.

Baseline demographic, clinical characteristics, PSH-AM score and outcome of the study population

Patients' age, gender, pre-operative GCS, and diagnosis, time from injury to surgery, type of surgery, day of sedation, the ratio and the PSH-AM score of the patients who met the criteria of "probable", "probable" and "unlikely", the NICU and Hospital stays, and GOS at discharge and after three months.

Variables	Total	Dexmedetomidine group	Control group	p vaule
Demographic				
No. of patients	90	50	40	-
Male gender	62 (68.9%)	37 (74%)	25 (62.5%)	0.242
Age, Mean±SD, y	46.76±15.41	47.50±15.12	45.83±15.92	0.611
Preoperative GCS, Mean±SD	6.26±1.77	6.24±1.88	6.28±1.65	0.926
Diagnosis				
Cerebral contusion without hemorrhage	23 (25.6%)	14 (28%)	9 (22.5%)	0.552
Hemorrhagic cerebral contusion	54 (60%)	30 (60%)	24 (60%)	1
Acute subdural hematoma	72 (80%)	38 (76%)	34 (85%)	0.289
Acute epidural hematoma	35 (38.9%)	19 (38%)	16 (40%)	0.847
Skull fracture	65 (72.2%)	36 (72%)	29 (72%)	0.958
Subarachnoid hemorrhage	78 (86.7%)	43 (86%)	35 (87%)	0.835
Cerebral hernia	30 (33.3%)	14 (28%)	16 (40%)	0.23
Time from injury to surgery	5.21±1.75	5.03±1.76	5.43±1.71	0.89
Type of surgery				
Decompressive craniectomy	87 (96.7%)	48 (96%)	39 (97.5%)	1
Epidural hematoma clearing	35 (38.9%)	19 (38%)	16 (40%)	0.847
Subdural hematoma clearing	72 (80%)	38 (76%)	34 (85%)	0.289
Hemorrhagic contusion clearing	47 (52.2%)	25 (50%)	22 (55%)	0.637
Lateral ventriculopuncture drainage	90 (100%)	50 (100%)	40 (100%)	1
Day of sedation	5.73±2.88	5.46±2.82	6.08±2.95	0.317
PSH diagnostic likelihood	6.73±6.58	5.26±4.66	8.58±8.09	0.017
Probable (≥17)				
No.	11 (12.2%)	3 (6%)	8 (20.0%)	0.056
Score	21.45±3.27	18.33±1.53	22.63±2.97	0.045
Possible (8-16)				
No.	12 (13.3%)	5 (10%)	7 (17.5%)	0.358
Score	11.17±2.69	10.80±3.56	11.43±2.15	0.710
Unlikely (<8)				
No.	67 (74.4%)	42 (84%)	25 (62.5%)	0.028
Score	3.52±2.35	3.67±2.40	3.28±2.30	0.519
NICU stay, Mean±SD, d	17.90±14.93	15.70±13.07	20.65±16.74	0.119
Hospital stay, Mean±SD, d	25.87±18.40	23.50±16.58	28.53±20.28	0.174
GOS at discharge	2.89±1.22	3.00±1.28	2.75±1.15	0.338
GOS after 3 months	3.25±1.46	3.42±1.47	3.05±1.43	0.234

Note: P Values for differences between two treatment groups by Student t test or Fisher's exact test.