



# Investigation of the optimal duration of bed rest in the supine position to reduce complications after lumbar puncture combined with intrathecal chemotherapy: a multicenter prospective randomized controlled trial

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## Abstract

**Purpose** This randomized, open-label trial was conducted to investigate the optimal duration of bed rest after intrathecal chemotherapy to reduce the incidence of complications without increasing patients' tolerance to long-term bed rest.

**Methods** A total of 390 patients receiving intrathecal chemotherapy were randomly assigned 1:1:1 to undergo bed rest for 6, 8, or 10 h after intrathecal chemotherapy. The primary outcome was the rate of complications after intrathecal chemotherapy. The analysis was per protocol.

**Results** A total of 359 patients among the 390 patients in our study completed follow-up with 120 patients in the 6-h group, 120 in the 8-h group, and 119 in the 10-h group. The complications among the three groups differed significantly ( $P = 0.005$ ). The 6-h group had significantly more complications than the 8- (50, 41.7% vs 29, 24.2%,  $P = 0.004$ ) and 10-h groups (50, 41.7% vs 31, 26.1%,  $P = 0.011$ ), whereas the difference between the 8- and 10-h groups was not significant (29, 24.2% vs 31, 26.1%,  $P = 0.737$ ).

**Conclusions** The overall results support that the optimal time interval for bed rest in the supine position after intrathecal chemotherapy is 8 h. This trial is registered with the Chinese Clinical Trial Registry (number ChiCTR-IOR-17011671).

**Keywords** Complications after intrathecal chemotherapy · Lumbar puncture · Bed rest time · Tolerance to long-term bed rest

## Introduction

Acute leukemia (AL) is a malignant disease derived from hematopoietic stem cells [1]. Because most systemic chemotherapeutic agents cannot pass through the blood-brain barrier, the central nervous system (CNS) becomes a sanctuary for leukemia cells. Since the 1970s, the use of lumbar puncture combined with intrathecal chemotherapy has played a major role in controlling CNS involvement, and the efficacy of treatment for AL has greatly improved over the past 30 years [2, 3].

Lumbar puncture (LP) is an invasive procedure. This procedure is indicated for diagnostic LP, spinal anesthesia, and

intrathecal chemotherapy. Life-threatening adverse events due to the procedure are rare [4], but less severe complications may be common, such as post-lumbar puncture headache (PLPH), back pain, nausea/vomiting, lower extremity discomfort, infection, and bleeding [5]. These complications can result in discomfort for patients and can cause them to fear the procedure. The mechanism of complications associated with LP is currently unclear. Most researchers suggest that complications such as PLPH are associated with intracranial hypotension caused by leakage of cerebrospinal fluid (CSF) from the puncture site [6–8].

To minimize the complications associated with LP, bed rest after LP is generally recommended. In 1899, Bier first recommended prophylactic bed rest in a supine position after LP to prevent complications, because rest in the supine position reduced CSF pressure, suppressed CSF leakage after LP, and accelerated healing of the puncture holes in the dura mater [9]. Currently, bed rest following LP is a common practice at many facilities. The typical bed rest duration is 6 h, which is

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the interval recommended by neurologists and anesthetists and required in hematology departments [10–13].

However, clinical practice and studies have shown that in contrast to neurological patients with a single diagnostic LP, multiple LPs for intrathecal chemotherapy are part of standard treatment protocols for hematology-oncology patients. Repeated punctures and intrathecal chemotherapy can delay the healing of the puncture holes and increase the CSF leakage, which likely increases the incidence of complications [1, 14].

Therefore, following the neurological standard (i.e., 6 h of bed rest in the supine position after LP) may not effectively control the incidence of complications after intrathecal chemotherapy. Our hypothesis is that increasing the bed rest time after intrathecal chemotherapy will be associated with a reduction in the incidence of PLPH and other related complications. However, prolonged bed rest in the supine position can also decrease the degree of tolerance and lead to many discomforts for the patients, such as urinary retention, insomnia, bedsores, and thrombosis [15]. The absence of a research-based optimal standard for bed rest after intrathecal chemotherapy prompted the development of this study. A multicenter, randomized, open-label trial was conducted to determine the effectiveness of various rest times in the supine position (6, 8, and 10 h) for reducing the incidence of complications after intrathecal chemotherapy.

## Methods

### Study design

This study was a multicenter, randomized, open-label trial that selected hematological patients who underwent LP combined with intrathecal chemotherapy at the First Affiliated Hospital of Sun Yat-sen University, the Second Affiliated Hospital of Sun Yat-sen University, the First People's Hospital of Foshan, and the Affiliated Hospital of Guilin Medical University between January 1, 2016, and July 1, 2017. Ethical approval was obtained from the clinical research and experimental animal ethics committees of the four hospitals.

### Patients

The inclusion criteria for the eligible patients were as follows: more than 14 years of age and indications for the prevention or treatment of CNS involvement caused by hematological diseases. The following patients were excluded: those with contraindications for LP and intrathecal chemotherapy [16], those with pre-existing headaches and other discomforts, those with unsuccessful LP, and those who failed to complete the required rest time in the supine position without authorization. All included patients signed the informed consent form.

## Randomization and masking

In this study, randomization was accomplished by assigning a number to each patient at the beginning of the study using a sequence generated by computer. Then, the patients were randomly allocated to three groups according to their assigned number in a 1:1:1 ratio. The three groups were required to rest in the supine position without a pillow for 6, 8, or 10 h after intrathecal chemotherapy. The randomization was performed by a researcher of the Department of Hematology, the First Affiliated Hospital of Sun Yat-sen University, who was not included in the rest of the trial. The clinicians who performed the LP enrolled the participants, and a specialized staff assigned them to the trial groups. The trial was open label for the patients and clinicians because the patients were informed of the exact bed rest duration; thus, masking the bed rest time for the clinicians was not possible.

## Procedures

All clinicians underwent training on the standard LP method before participating in the study. The standard LP method [17] was performed in the lateral recumbent position. A 22-G Quincke needle (Foshan, Guangdong, China) was inserted into the interspace between L3 and L4 or between L4 and L5, and the beveled edge of the needle was kept parallel to the longitudinal ligament. After the CSF opening pressure was measured, and 3–4 mL of CSF was extracted for examination. Then, a triple therapy [18] (10 mg of methotrexate, 50 mg of cytosine arabinoside, and 5 mg of dexamethasone) was administered intrathecally to each patient. The patients were required to rest in the supine position without a pillow for 6, 8, or 10 h, and the clinicians monitored the participants to ensure the timing of bed rest was accurate according to the protocol.

## Outcomes

After intrathecal chemotherapy, the demographic information and clinical characteristics of the patients were recorded, including sex, age, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) score [19], diagnosis at admission, CNS involvement history, incidence of repeated punctures in 1 week, previous history of PLPH or other complications, puncture level, incidence of repeated attempts to obtain a successful LP, CSF pressure, and CSF profiles.

The patients were followed up by phone call 7 days after the procedure to collect information regarding complications associated with the LP. The complications reported in the literature included PLPH, back pain, nausea/vomiting, lower extremity discomfort, spinal hematoma, iatrogenic meningitis, and brain herniation. The diagnosis of PLPH was made according to the International Classification of Headache Disorders (ICHD)-2 criteria [20]. PLPH is characterized by

the onset of headache within 5 days after LP. Headache often presents in the forehead and occiput and worsens after the patient is in an upright position for 15 min but can be relieved after the patient assumes the supine position for 15 min. PLPH is often combined with other non-specific symptoms, including nausea, vomiting, neck stiffness, photophobia, and tinnitus, and headache is normally relieved within 7 days or within 48 h after effective treatment of CSF leakage.

Additionally, researchers surveyed the degree of tolerance to remain in bed for an extended time among the patients of the three groups using a visual analog scale (VAS) [21] ranging from 0 to 10 points, with 0 points indicating no tolerance at all and 10 points indicating complete tolerance.

### Statistical analysis

SPSS 22.0 was used for the statistical analysis. The chi-square test was used to compare ratios. The Bonferroni method was used to correct the level of significance for the pairwise comparison of ratios among groups. An analysis of variance (ANOVA) was used for comparisons of measurement data among multiple groups, and the least significant difference (LSD) test was used for pairwise comparisons of multiple

groups. The nonparametric Mann-Whitney  $U$  test was used to analyze the measurement data without a normal distribution. Logistic regression analysis was used to evaluate the risk factors that affected the complications. A value of  $P < 0.05$  was considered statistically significant.

### Results

A total of 390 subjects were recruited from the hematology departments of four hospitals; the study included 359 procedures performed on 189 patients. The 6-, 8-, and 10-h groups contained 120, 120, and 119 individuals, respectively (Fig. 1). Of the 359 subjects, 56.5% were males, and 43.4% were females. The average age was 34.9 years, with a range from 15 to 68 years. The average BMI was 21.2 kg/m<sup>2</sup>. The diagnoses of the patients included 123 individuals (32.3%) with acute lymphoblastic leukemia (ALL), 155 individuals (43.2%) with acute myelocytic leukemia (AML), 48 individuals (13.4%) with non-Hodgkin's lymphoma (NHL), 25 individuals (7.0%) with lymphoma cell leukemia (LCL), 4 individuals (1.1%) with chronic granulocytic leukemia (CML), 3 individuals (0.8%) with chronic myelomonocytic leukemia, and 1

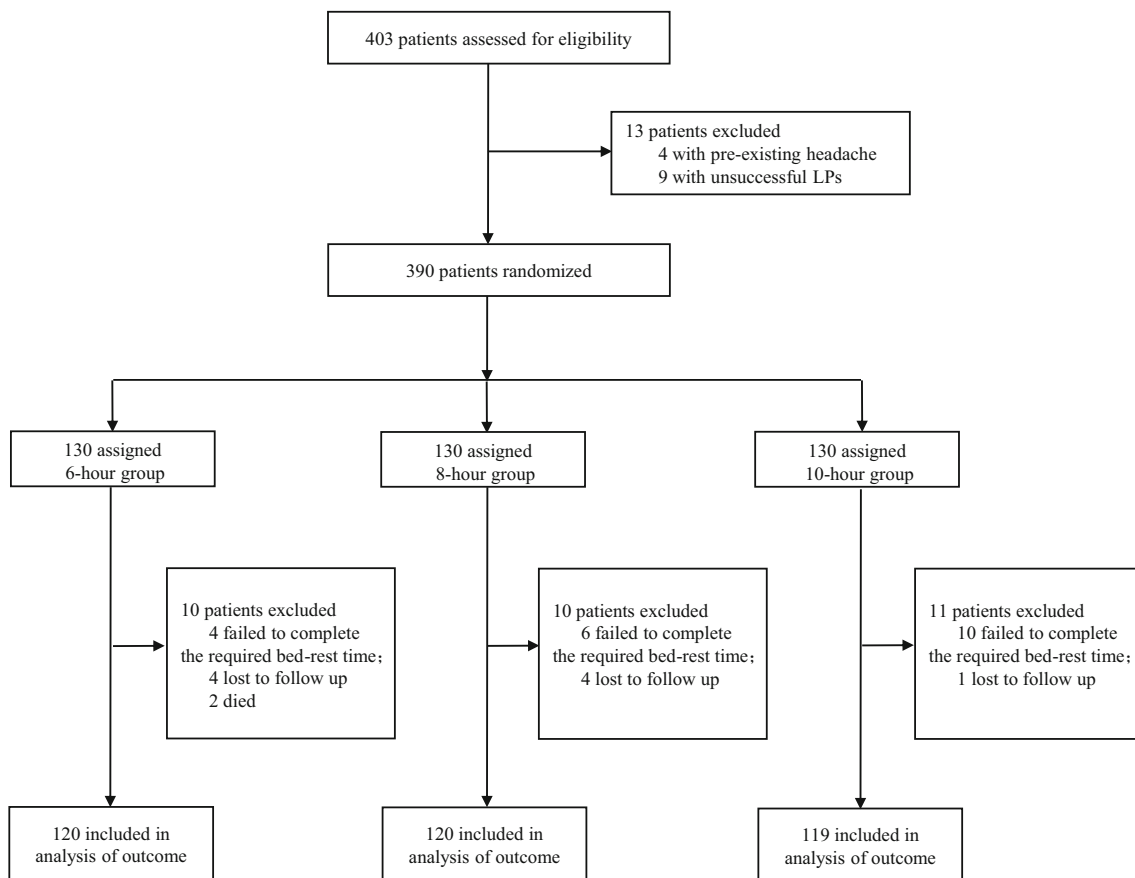


Fig. 1 Trial profile

individual (0.3%) with myeloid sarcoma. A total of 39 individuals (10.9%) underwent LP for therapeutic purposes, and 320 patients (89.1%) underwent LP for prophylactic purposes. A total of 235 individuals (65.5%) had a previous LP history. The differences in the demographic and clinical characteristics of the three groups were not significant (Table 1).

For the 359 procedures, complications associated with the LP combined with intrathecal chemotherapy were recorded on 110 occasions (39.6%). The incidence of complications was 41.7% (50) in the 6-h group, 24.2% (29) in the 8-h group, and 26.1% (31) in the 10-h group. The difference among the three groups was significant ( $P = 0.005$ ). The 6-h group had significantly more complications than the 8-h ( $P = 0.004$ ) and 10-h groups ( $P = 0.011$ ), whereas the difference between the 8- and 10-h groups was not significant ( $P = 0.737$ ) (Fig. 2).

The different complications after intrathecal chemotherapy were grouped as four clinical events as follows: PLPH (57, 15.9%), back pain (54, 15.0%), nausea/vomiting (27, 7.5%), and lower extremity discomfort (22, 6.1%) (Table 2). The most common complication was PLPH. The incidence rates of PLPH were 25.8% (31) in the 6-h group, 9.2% (11) in the 8-h group, and 12.6% (15) in the 10-h group. A significant difference was observed among the three groups ( $P = 0.001$ ). The 6-h group had a significantly higher rate of complications

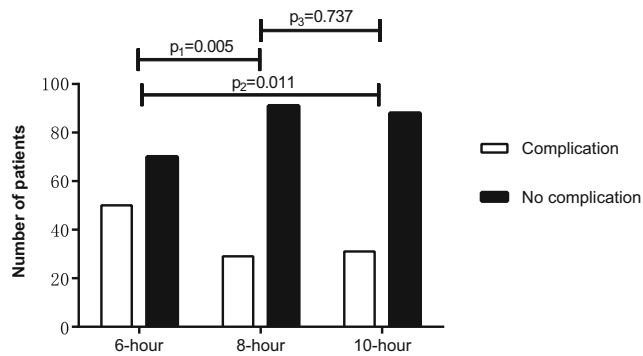
than the 8-h group ( $P = 0.001$ ) and the 10-h group ( $P = 0.009$ ), whereas the difference between the 8- and 10-h groups was not significant ( $P = 0.393$ ). Additionally, the incidence rates of back pain, nausea/vomiting, and lower extremity discomfort showed no significant differences among the 6-, 8-, and 10-h groups.

A total of 110 of the 359 subjects developed complications after intrathecal chemotherapy. Table 3 shows a comparison of the clinical and demographic characteristics between patients with and without complications. In the multivariate analysis of risk factors for complications using the same standardized procedures, insufficient bed rest time, repeated punctures in 1 week, CNS involvement, L3–4 puncture level, and repeated attempts to achieve a successful LP were significant independent risk factors for complications after intrathecal chemotherapy (Table 4).

In this study, the degree of tolerance of bed rest was evaluated using VAS scores among the patients in the 6-, 8-, and 10-h groups. The difference in the degree of tolerance among the three groups was significant ( $P < 0.0001$ ). The average VAS score of the 6-h group was 7.31, with a range from 5 to 9 points. The average VAS score of the 8-h group was 7.08 points, with a range from 4 to 8 points. Finally, the average VAS score of the 10-h group was 5.04 points, with a range

**Table 1** Demographic and clinical characteristic of the 6-, 8-, and 10-h groups

Profile	6-h group ( $n = 120$ procedures on 94 patients)	8-h group ( $n = 120$ procedures on 87 patients)	10-h group ( $n = 119$ procedures on 82 patients)	$P$ value
Sex				0.571
Male	69 (57.5%)	70 (58.3%)	64 (53.8%)	
Female	51 (42.5%)	50 (41.7%)	55 (46.2%)	
Mean (SD) age (years)	36.76 (14.0)	35.35 (14.21)	32.59 (14.92)	0.076
Mean (SD) BMI ( $\text{kg}/\text{m}^2$ )	21.81 (3.17)	21.08 (3.61)	20.65 (2.79)	0.080
Diagnosis				0.834
ALL	36 (30.0%)	40 (33.3%)	47 (39.5%)	
AML	52 (43.3%)	53 (44.2%)	50 (42.0%)	
NHL	18 (15.0%)	17 (14.2%)	13 (10.9%)	
LCL	11 (9.2%)	8 (6.7%)	6 (5.0%)	
Others	3 (2.5%)	2 (1.7%)	3 (2.5%)	
Purpose of LP				0.242
Therapeutic	13 (10.8%)	9 (7.5%)	17 (14.3%)	
Prophylactic	107 (89.2%)	111 (92.5%)	102 (85.7%)	
Repeated puncture in 1 week	19 (10.0%)	13 (10.8%)	15 (12.6%)	0.808
Pre-history of complications	17 (14.2%)	18 (15.0%)	18 (15.1%)	0.974
Puncture level				
L3–4	48 (40.0%)	43 (35.8%)	45 (37.8%)	0.801
L4–5	72 (60.0%)	77 (64.2%)	74 (62.2%)	
First puncture succeeded	98 (81.7%)	95 (79.2%)	96 (80.7%)	0.886
Mean (SD) CSF pressure ( $\text{mmH}_2\text{O}$ )	154.65 (41.71)	157.14 (45.91)	153.76 (41.27)	0.820
Mean (SD) CSF protein ( $\text{mg}/\text{L}$ )	417.76 (180.34)	401.57 (183.82)	443.21 (203.80)	0.268



**Fig. 2** Complications following intrathecal chemotherapy among the three groups.  $p_1$  showed the  $P$  value between 6- and 8-h groups,  $p_2$  showed the  $P$  value between 6- and 10-h groups, and  $p_3$  showed the  $P$  value between 8- and 10-h groups. The Bonferroni method was used to correct the level of significance for the pairwise comparison of ratios among groups; the significant level was corrected to 0.0167

from 2 to 7 points. The difference between the 6- and 8-h groups was not significant ( $P = 0.073$ ); however, the difference between the 6- and 10-h groups was significant ( $P < 0.0001$ ).

## Discussion

In our study, the overall rate of complications after intrathecal chemotherapy was 30.6%. The types of complications mainly included PLPH, back pain, nausea/vomiting, and lower extremity discomfort, which were consistent with previous reports. Of these complications, PLPH was the most common complication after intrathecal chemotherapy [7], with an incidence of 15.9%. Bleeding, infection, chemical meningitis, and other severe complications were not present in this study; however, because the incidence rates of PLPH and other complications were relatively high, the therapeutic compliance and disease prognosis of the patients was severely affected. This finding highlights an urgent clinical issue that needs to be addressed immediately.

Patients undergoing treatment for hematological disease often undergo multiple LPs, which increase their risk for PLPHs and other related complications. Currently, no guidelines are available regarding the optimal duration of bed rest for the prevention of complications in patients with intrathecal chemotherapy. We performed a multicenter, randomized,

open-label study to investigate the optimal standard bed rest time after intrathecal chemotherapy to reduce the incidence of complications. Our hypothesis was that 8 h of bed rest could decrease the perceptions of complications and would produce no significant changes in the tolerance of patients compared to the neurological institution's standard of 6 h. Therefore, we divided the enrolled subjects into three groups who rested 6, 8, and 10 h in the supine position after intrathecal chemotherapy.

Our data showed that the incidence of complications significantly differed among the three groups. Compared to the standard of 6 h of bed rest after LP, the additional 2 to 4 h of bed rest in the 8- and 10-h groups contributed to a significant reduction in the perception of all complications, especially PLPH. The mechanism is consistent with Bier's hypothesis that the continued CSF leakage through the puncture site can lead to CSF accumulation and the reduction of CSF pressure, which is an important factor for complications. Lying in the supine position after LP could suppress the leakage of the CSF and accelerate the healing of the dural tear, which could effectively reduce the incidence of PLPH and other complications. Although vomiting and back pain were also related to the variation in CSF volume, no significant difference was observed among the three groups in our study. Intrathecal chemotherapy-associated toxicity characterized by vomiting and back pain due to local trauma was also taken into account.

Although the above results demonstrated that prolonged bed rest could reduce the incidence of complications, many studies showed that the bed rest time was not the only contributing factor [22]. Other risk factors, including sex [23], age, needle size, puncture direction, LP position, and the experience of the operator, were reported in previous studies [24, 25]. In our study, the risk factors for complications after intrathecal chemotherapy were analyzed using the same standardized procedures and a 22-G needle size [26].

In terms of non-modifiable factors, patients who underwent multiple LPs in 1 week developed more complications than those who underwent only one LP. This result was consistent with previous studies [27, 28]. For the first time, we found that CNS involvement was associated with an increased risk of complications. The difference in the incidence of complications may have occurred because patients with CNS involvement are subjected to increased intrathecal chemotherapy, and CNS involvement can cause changes in the composition and generation of the CSF, thereby affecting CSF leakage.

**Table 2** Types of complications following intrathecal chemotherapy in the 6-, 8-, and 10-h groups

	6-h group ( $n = 120$ )	8-h group ( $n = 120$ )	10-h group ( $n = 119$ )	$P$ value
Overall complications	50 (41.7%)	29 (24.2%)	31 (26.1%)	0.005
PLPH	31 (25.8%)	11 (9.2%)	15 (12.6%)	0.001
Back pain	15 (12.5%)	18 (15.0%)	21 (17.6%)	0.538
Nausea/vomiting	12 (10.0%)	8 (6.7%)	7 (5.9%)	0.439
Lower extremity discomfort	9 (7.5%)	7 (5.8%)	6 (5.0%)	0.720

**Table 3** Comparison of demographic and clinical characteristics between patients with and without complications following intrathecal chemotherapy

	With complications ( <i>n</i> = 110)	Without complications ( <i>n</i> = 249)	<i>P</i> value
Bed rest time			0.001
6 h	50 (45.5%)	70 (28.1%)	
More than 6 h	60 (54.5%)	179 (71.9%)	
Sex			0.058
Male	54 (49.1%)	149 (59.8%)	
Female	56 (50.9%)	100 (40.2%)	
Age			0.090
≤ 50 years	82 (74.5%)	205 (82.3%)	
> 50 years	28 (25.5%)	44 (17.7%)	
BMI			0.677
< 24 kg/m <sup>2</sup>	84 (76.4%)	185 (74.3%)	
≥ 24 kg/m <sup>2</sup>	26 (23.6%)	64 (25.7%)	
With CNS involvement	21 (19.1%)	18 (7.2%)	0.001
Previous history of complications	20 (18.2%)	33 (13.3%)	0.225
Repeated puncture in 1 week	19 (17.3%)	21 (8.4%)	0.014
Puncture level			0.008
L3–4	53 (48.2%)	83 (33.3%)	
L4–5	57 (51.8%)	166 (66.7%)	
First puncture succeeded	81 (73.6%)	208 (83.5%)	0.029
CSF pressure (mmH <sub>2</sub> O, min-max)	150 (50 to 330)	155 (78 to 375)	0.292
CSF protein			0.010
≤ 450 mg/L	60 (54.5%)	171 (68.7%)	
> 450 mg/L	50 (45.5%)	78 (31.3%)	

In terms of modifiable factors other than the bed rest time, the experience level of the clinician is a major factor affecting the incidence of complications. The present study showed that a successful first attempt to achieve LP reduced the incidence of complications. Additionally, during the LP procedure, the puncture needle can be inserted into the L3–4 or L4–5 intervertebral space according to the LP guidelines. However, our multivariate logistic regression analysis showed that the incidence of complications after intrathecal chemotherapy was increased when the needle was inserted into the L3–4 intervertebral space. We suggest that this increase may be due to the narrower intervertebral space at L3–4 compared to the L4–5 space, which increases the difficulty of the puncture.

Moreover, the L3–4 position is higher than that of L4–5; therefore, the CSF pressure is higher, which tends to cause an increase in CSF leakage.

Because the incidence of complications after intrathecal chemotherapy is influenced by multiple factors, prolonged bed rest cannot thoroughly eliminate the related complications. The results from our study also showed no significant difference in the incidence of complications after 10 h of bed rest compared to 8 h of bed rest.

Furthermore, prolonged bed rest in the supine position is difficult for many patients [29], who frequently complain of many discomforts, such as bedsores, deep vein thrombosis, pneumonia, and difficulty in urination, eating, and falling

**Table 4** Logistic regression analysis of variables in patients with and without complications following intrathecal chemotherapy

	<i>P</i> value	OR	95% CI
Non-modifiable factors			
CNS involvement	0.002	3.144	1.504 to 6.574
Repeated punctures in 1 week	0.013	2.538	1.217 to 5.292
Modifiable factors			
Bed rest time	0.001	2.288	1.403 to 3.745
Repeated attempts to achieve a successful LP	0.021	1.958	1.106 to 3.467
Puncture level	0.041	1.667	1.020 to 2.725

asleep. Recently, an increasing number of studies have suggested decreasing the amount of bed rest time after LP and leaving the bed earlier [10, 30]. Therefore, determining the optimized rest time in the supine position that leads to the fewest complications in patients and that is tolerated best by patients is a priority.

This study compared the degrees of tolerance of patients in the three groups with different durations of bed rest. Compared to the institution's standard of 6 h of bed rest, an additional 2 h of bed rest in the 8-h group produced no significant differences in the patients' degrees of tolerance, whereas an additional 4 h of bed rest in 10-h group significantly decreased the patients' degrees of tolerance. Furthermore, we found during follow-up that the incidence of withdrawal from the study was highest in the patients in the 10-h group due to their inability to tolerate the prolonged bed rest, which from another perspective could also suggest that the degree of tolerance was lower for the patients in the 10-h group for the bed rest time.

In conclusion, the incidence of complications after intrathecal chemotherapy was significantly decreased when the bed rest time in the supine position was extended from 6 h to 8 or 10 h. However, the duration of bed rest is not the only factor that affects the occurrence of complications. Extension of the bed rest time in the supine position from 8 to 10 h did not significantly decrease the incidence of complications. Moreover, the degree of tolerance of patients who rested in bed for 10 h was significantly lower than in those who rested in bed for 6 h. In contrast, when comparing 8 to 6 h of rest, a significant difference was observed in the degree of patient tolerance. Therefore, our findings support that the optimal time for bed rest in the supine position after intrathecal chemotherapy is 8 h.

Furthermore, the limitation of this study is that all the lumbar punctures were performed by the same needle, 22 G in size. Some studies showed that the incidence of complications may be reduced by a smaller needle. The optimal time for bed rest may be shortened using the smaller needle compared with the 22-G needle size. Further research is needed.

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### Compliance with ethical standards

This study was approved by the clinical research and experimental animal ethics committees of the First Affiliated Hospital of Sun Yat-sen University, the Second Affiliated Hospital of Sun Yat-sen University, the First People's Hospital of Foshan, and the Affiliated Hospital of Guilin Medical University. All patients gave written informed consent.

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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