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Research Article

Comparative Evaluation of Two Different Doses of Pre-Emptive Oral Pregabalin on Duration of Spinal Anesthesia and Postoperative Pain

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ABSTRACT

Background: Pregabalin provides good postoperative analgesia in nociceptive stimuli. Various studies show that preemptive oral pregabalin reduces acute postoperative pain. We conducted a study to evaluate the efficacy of two different doses of pregabalin and its effect on onset and duration of spinal anesthesia and postoperative pain.

Methods: In prospective, double-blind and randomized study, 60 patients posted for vaginal hysterectomy under spinal anesthesia were randomly allocated to two groups recieving cap. Pregabalin 75 mg (group 1) and cap pregabalin 150 mg (group 2) orally, 90 min prior to surgery. Onset and duration of motor and sensory blockade were observed. Postoperative pain was assessed by VAS for 24 hrs. Injection paracetamol 1 gm. was given intravenously as rescue analgesic. Time of first rescue analgesic and total dose of rescue analgesics was noted.

Results: Group 2 patients had better postoperative analgesia in terms of prolonged sensory and motor blockade which correlated well with the time of first request for rescue analgesia (504±123.2 min) as compared to group 1 patients (304.9±37.6 min). Also the total dose of rescue analgesic (paracetamol) was significantly less with 150mg pregabalin ($p = 0.0001$).

Conclusion: Pregabalin 150 mg prolongs the duration of spinal anesthesia and has better analgesic profile without significant side effects. Thus we conclude that 150 mg pregabalin given preemptively optimizes spinal anesthesia well in patients for vaginal hysterectomy.

Spinal anesthesia is the commonest technique used for gynecological procedures. Various adjuvants so far have been used to prolong the duration of spinal anesthesia, delaying the onset of post-operative pain and reducing opioids requirement [1]. Opioids play an important role in perioperative pain relief but have their own limitations (PONV, reduced respiratory drive and sedation).

Pain is a predictable part of the postoperative experience but if inadequately managed then can have profound implications. It may produce clinical and psychological changes which in turn will increase morbidity and mortality. Hence optimum treatment with minimal side effects is essential to encourage early mobility and maximal functional recovery. Nowadays a multimodal approach which includes NSAIDS and opioids is considered for treating postoperative pain. Better understanding of pain pathways and physiology has led to emergence of the new concept of preemptive analgesia developed by Crile and is a method of administration of medications before surgery to prevent establishment of central sensitization of pain and reduces intensity and duration of postoperative pain [2].

Pregabalin is a gamma amino butyric acid analogue which binds to the α2-δsubunits of presynaptic voltage gated calcium channels. It achieves its analgesic effect by

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developing hyperplastic changes at the surgical site which are triggered by noxious stimuli. It also desensitizes the central neural system which in turn prevents further amplification of noxious impulses from the surgical site [3-4]. It is rapidly absorbed orally and achieves plasma level within 30 min to 2 hrs and has common side effects like dizziness and somnolence.

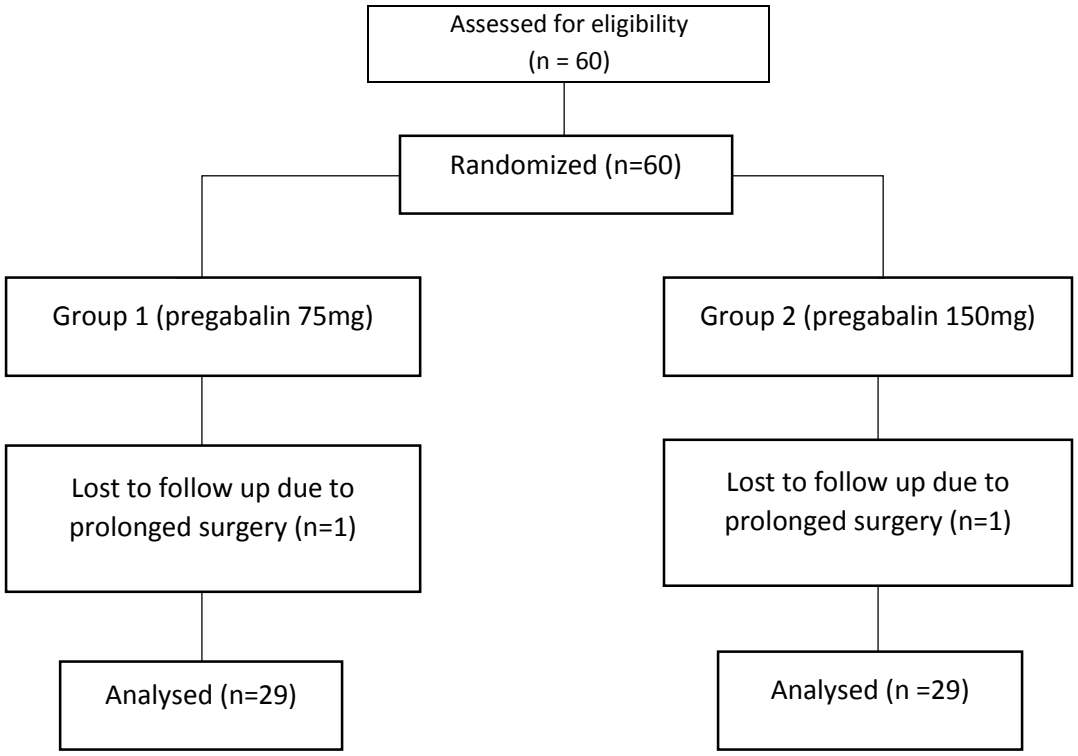
Various studies have been conducted using pregabalin as premedication in different doses (75-300mg) to study its effect on the duration of postoperative analgesia following spinal anesthesia. But most of the studies compared pregabalin with either placebo or other drugs. A higher dose (300mg) was reported to be associated with increased levels of sedation. Very few studies have compared efficacy of two different doses of pregabalin premedication on characteristics of bupivacaine spinal anesthesia and postoperative pain profile.

We hypothesize that pregabalin pretreatment could prolong the duration of subarachnoid block. Hence, we designed this prospective randomized double-blind study to compare and evaluate the efficacy of two different doses of pregabalin pretreatment on characteristics of spinal anesthesia. Onset and duration of sensory and motor block and time to first request for rescue analgesic was considered as primary outcome. 24 hrs total analgesic requirement and side effects were recorded as secondary outcome.

Methods

After obtaining institutional ethical committee approval (ECR/275/Inst/MH/2013/RR-16), a prospective, randomized and double-blind study was conducted on 60 patients scheduled for vaginal hysterectomy under spinal anesthesia. Written informed consent was obtained from all patients. The visual analogue scale (VAS) was explained to the patients in preoperative visit. Patients in the age group of 35 to 65 years, American society for anesthesiologists (ASA) physical status of I, II and body mass index (BMI) of 18–35 kg/cm2 posted for vaginal hysterectomy under spinal anesthesia were included. Patients with refusal to participate in the study, use of anti-anxiety drug, history of drug/alcohol abuse, history of chronic pain and daily intake of analgesic drugs, history of epilepsy, failed spinal anesthesia and any contraindication to spinal anesthesia were excluded from study.

Figure 1- Cohort flow chart of study



The study subjects were allocated into 2 groups of 30 each using a computer-generated random list. Both patient and anesthesiologist were blinded to treatment and all observations were recorded by anesthesiologist

blinded to study groups. Doctor who was not involved in perioperative evaluation administered the capsule with sips of water, according to randomization sequence.

Ninety minutes before surgery, group I patients received capsules pregabalin 75 mg and group II patients received Cap pregabalin 150 mg in preoperative room. Electrocardiography, blood pressure, and oxygen saturation were monitored upon arrival to the operating room and subsequently every 5 minutes. Intravenous crystalloid (Ringer's lactate) was administrated at 10mL/kg. All patients received spinal anesthesia with 3mL of 0.5% hyperbaric bupivacaine through the L 3 - L 4 interspace via midline approach with a 26-G Quincke's needle in sitting position.

Sensory block was assessed using pin prick method in midaxillary line on both sides of chest every 1 minute until maximum sensory blockade was achieved in relevant body segment and subsequently every 5 minutes for next 30 minutes. Later assessment was performed every 15min until recovery of sensation in L2 segment. The onset of sensory block was defined as time between subarachnoid injection and reaching sensory level up to T10.Time to two segment regression of sensory block was calculated as time interval between reaching the highest sensory level and two segment regression of this level. Time to regression to L2 was calculated as interval between maximum sensory level and time to reach second lumbar segment.

Motor block was assessed by modified Bromage scale. Modified Bromage Scale: 0 - No motor impairment, 1- Unable to raise either extended leg, 2 - Unable to raise either leg, flex knee, able to move ankle joint, 3 - Unable to move knee & Foot. Time interval between subarachnoid injection and reaching a Bromage score 1 was recorded as motor onset. Motor block duration was defined as time from spinal block to return to Bromage score 0.

Intraoperative decrease in mean arterial pressure less than 20% of the baseline was defined as hypotension and treated with injection mephentermine 6 mg intravenous or crystalloids. Decrease in heart rate less than 45 beats per min was defined as bradycardia and treated with Inj. atropine 0.6 mg intravenously.

Postoperative pain was assessed by visual analog scale (0= no pain, 10=worst possible pain). Patients with VAS≥4 were treated with injection paracetamol 1gm intravenously as rescue analgesic. If after paracetamol patient still complained of pain then it was treated with injection tramadol 50mg intravenously. Time to first rescue analgesic and number of doses required over 24 hrs was recorded.

Ramsay sedation score (scale of 1-6) was used to assess sedation in all study population. Sedated patients were closely observed with pulse oximetry and managed appropriately as per requirement. Presence of any complications like dizziness, dry mouth or nausea and vomiting were recorded. Post operatively VAS, sedation score and vital parameters (MAP and HR) were monitored at 1, 2, 4, 6, 12 and 24 hrs.

Statistical Analysis:

Sample size was calculated with power of 80% and α value to 0.05 for comparing the means in two groups (pregabalin 75mg and pregabalin 150 mg) with anticipated standard deviation being 3.2 and difference between the means as 2.4. The calculated sample size for each group came up to 24. Hence, we allocated 30 patients in each group considering the dropouts.

Data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL). Demographic data and clinical variables were compared using the Student t test, X2 test, or Mann–Whitney–Wilcoxon test as appropriate. Continuous parameters such as age, BMI, surgery time, time of the first request for analgesics and the duration of sensory and motor blockade were compared between 2 groups using the unpaired Student t test. Categorical scales such as adverse effects and the number of postoperative analgesics were analyzed using Fisher test. Associations between the duration of the sensory blockade and the time to the first analgesic request and the total number of rescue analgesic doses during first 24 hours were analyzed using Pearson correlation. A P value < 0.05 was considered significant.

Results

58 patients completed the study according to the protocol and were in the analysis. 1 patient in each group lost to follow up because of prolonged surgery (Figure 1). When the two groups were compared in terms of age, BMI, ASA grades and duration of surgery, no significant difference was found (p>0.05) (Table1).

The mean time of onset for T10 sensory blockade was similar in both groups. The mean duration of time to 2 dermatome regression from peak sensory block in group 2 (88.8±13.1 minutes) was significantly longer than in group 1 (67.1±10.9 minutes) (P= 0.001) and also the time for regression to L2 sensory block was significantly prolonged in group 2. In addition, the regression time from Bromage score 1 to Bromage score 0 was prolonged in group 2 (200.0±16.4 minutes) than in group 1 (168.2±31.6 minutes) (P =0.001) (Table 2).

Over the period of 24hrs, VAS pain scores were significantly decreased in group 2compare to group 1 at both early and late postoperative period (Figure 2). The time to the first request for postoperative supplemental analgesia was significantly prolonged in group 2 (504.0±123.2 minutes) when compared with group 1 (304.9±37.6 minutes) (P=0.0001). The total doses of paracetamol required over 24hrs were lower in group 2 (P= 0.0001) (Table 3).

Table 1- Demographic characteristics

	Group 1 (n=29)	Group 2 (n=29)	P value
Age (years)	44.91±5.84	42.40±7.17	0.094
BMI (Kg/cm2)	23.29 ± 2.31	22.78 ± 2.28	0.4011
ASA grade: Class I	20(68.96%)	16(55.17%)	0.2834
Class II	9(31.03%)	13(44.82%)	0.2833
Duration of surgery(min)	107.18±5.06	106.85±9.86	0.8732

Notes: Data was presented as mean ± SD or as number and %. P represents comparison between two groups.

Table 2- Characteristics of sensory and motor block

Variables	Group 1(n=29) Mean ± SD	Group 2(n=29) Mean ± SD	P value
Time to T10 sensory block(min)	5.01 ±1.0	4.9±1.3	0.7044
Time to Bromage 1 block (min)	8.1 ±1.4	7.9±1.4	0.137
Time to 2 segment regression of sensory block (min)	67.1±10.9	88.8±13.1	0.0001
Time to sensory regression to L2 (min)	130.0±16.7	156.0±14.5	0.0001
Time to regress Bromage 0(min)	168.2±31.6	200.0±16.4	0.0001
Peak sensory level:	T6	T6	

Notes: Data was presented as mean ± SD or as number and %. P represents comparison between two groups

Figure 3- Post- Operative VAS scores

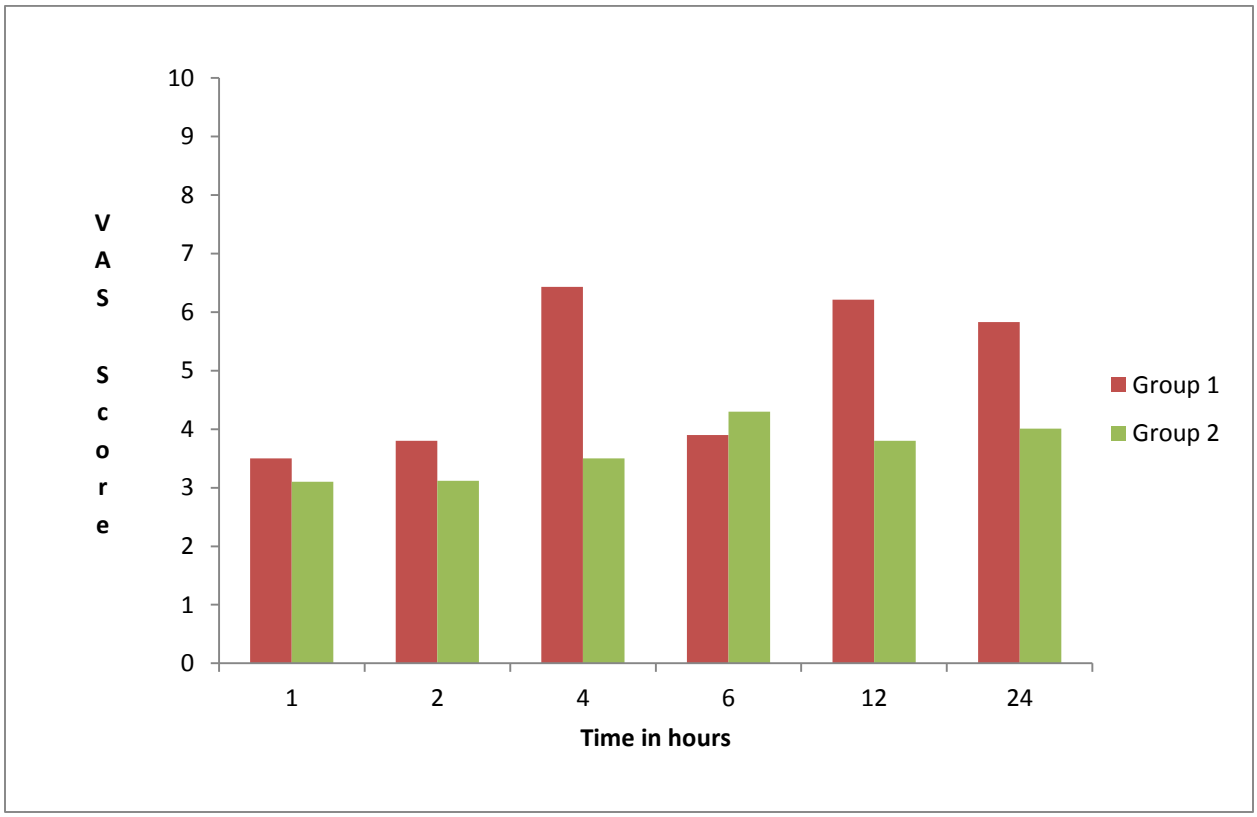


Table 3- Comparison of postoperative analgesia

	Group 1 (n=29) Mean ± SD	Group 2 (n=29) Mean ± SD	P value
Time to First analgesic request (min)	304.9±37.6	504 ± 123.2	0.0001
Total paracetamol dose (mg)	1500 ± 120	510 ± 105	0.0001

Notes: Data was presented as mean ± SD or as number and %. P represents comparison between two groups

The time for 2-dermatome regression from peak sensory block levels was positively correlated with the time to the first request for postoperative analgesics (P=0.0001) in both study groups. Prolonged postoperative analgesia in group 2 population helps to significantly reduce the total consumption of rescue analgesics in first 24 hours (P=0.0001).

Table 4 explains that sedation score was not significant in early and late postoperative period in both study groups. While mild sedation recorded in group II patients were statistically and clinically not significant.

Table 4- Sedation score at different time intervals

Time	Group 1 (n=29)	Group 2 (n=29)	P value
1hour	1.85 ± 0.50	2.06±0.24	0.046
2hours	1.48±0.57	1.53±0.12	0.643
6hours	0.67±0.37	0.89±0.23	0.008
12hours	0.27±0.27	0.30±0.21	0.638

Notes: Data was presented as mean ± SD or as number and %. P represents comparison between two groups

Discussion

We conducted this study to compare the effects of 75 mg and 150 mg of preemptive pregabalin on the characteristics of subarachnoid block and found an association with significantly prolonged two – segment sensory regression time and regression to spinal level L2 with 150 mg of pregabalin. Total duration of sensory and motor block was also prolonged in same group patients. In the postoperative period significantly improved VAS score and reduced rescue analgesics consumption were noted in patients who received 150mg pregabalin. However none of the doses affected the onset of sensory or motor blockade. There were no significant postoperative complications noted in either group.

The mechanism of prolongation of motor and sensory block by pregabalin pretreatment is not fully understood. Pregabalin, one of the gabapentenoids is gamma-amino butyric acid analogue that binds to α2-δsubunits of the voltage-gated calcium channels and decreases potassium mediated excitatory transmitter release [5]. Pregabalin modulates GABAnergic neurotransmission and calcium influx, hence exerting antiepileptic, anxiolytic and analgesic effects leading to better preoperative anxiety scores. Anxiolytic effects of pregabalin can be beneficial in reducing preoperative anxiety of the patients.

Earlier, several studies have demonstrated that pretreatment with pregabalin in variety of surgeries reduce postoperative VAS score [6-7]. To avoid bias in pain score we have included single surgical procedure. Vaginal hysterectomy is commonest gynecological procedure performed under neuraxial block with or without multimodal analgesia.

Cegin et al. studied preemptive use of pregabalin in infraclavicular blocks and reported an early onset of motor block and prolonged sensory block. In addition, first analgesic requirement time for group 150 mg and group 300 mg were significantly longer than that of group pregabalin 75 mg (p<0.005) [8]. While in our study there was no considerable difference in onset of motor and sensory block but the duration of both sensory and motor block was prolonged with 150 mg of pregabalin.

Park et al. reported in their study that 150 mg of pregabalin 2 hours before spinal anesthesia increases the duration of sensory and motor blockade (p=0.000). Time to first request analgesic in pregabalin 150mg group was (404.0+/-123.2 minutes) when compared with control group (204+/-37.6minutes) (p=0.000) [9]. Their result was consistent with our findings.

Bafna et al in their study compared the time to the first analgesic request in two study groups who received single dose 600mg gabapentin and 150mg pregabalin premedication in gynecological surgeries under spinal anesthesia [10]. In the pregabalin group, the analgesic effect was maintained for (535 ±32.8 min) which was similar to our study.

Rajappa G. et al. studied two doses of pregabalin (75mg and 150mg) with placebo as pre-emptive medication for post-operative pain relief in vaginal hysterectomy and found that both pregabalin groups had lower postop VAS score, decreased need of rescue analgesic and greater time for first rescue analgesic (P<0.001). 150 mg of pregabalin have better analgesic properties however its use may be limited due to increased incidence of dizziness. Hence they concluded that pregabalin 75mg could be the optimal preemptive dose [11]. The results were not consistent with our study results as we did not find any improvement with 75mg of pregabalin and also we did not find significant dizziness in patients pretreated with 150 mg pregabalin.

Monika k.et al compared two different doses (150 mg & 300mg) of pregabalin against placebo for surgeries under spinal anesthesia. They found that analgesic efficacy was similar and significant in both pregabalin groups but incidence of dizziness was more in patients

receiving pregabalin 300mg and concluded that pregabalin 150mg would be optimal preemptive dose for patients with vaginal hysterectomy under spinal anesthesia [12]. Our results are consistent with this study.

Hill et al in 2001 studied 300 mg pregabalin in dental surgical cases and noted many side effects such as PONV and dizziness [13]. They concluded 300mg pregabalin to be more effective than 50mg.

Ahis kalioglu et al used 150mg of pregabalin in double jaw surgery and reported improved postoperative analgesia [14].

Meta-analysis done by. Lam, D. M. et al included 74 studies and evaluated the analgesic efficacy of pregabalin in reducing post-surgical pain in terms of 2 and 24 hours VAS score and concluded that 2 hours VAS score was reduced in all procedures [6]. In our study VAS at early and late postoperative period was significantly lower in patients who received pregabalin 150mg pretreatment.

Meta-analysis by Yi-ming Wang et al. 2017 shows that pregabalin can reduce the occurrence of nausea and vomiting after abdominal hysterectomy.They agreed with the results of previous meta-analysis which state that use of pregabalin causes significant reduction in postoperative pain following different surgeries. They demonstrated that the use of pregabalin was associated with reduced pain scores at 2, 4 and 24hrs with rest and on mobilization, which is equivalent on a 110-point scale to VAS to 11.39 points at 2hours, 9.47 points at 4 hours and 5.55 points at 24hours at rest and 11.39 points at 2 hours, 4.32 points at 4hours and 5.55 points after mobilization. The cumulative morphine (rescue analgesic) consumption at 2, 12, 24, and 48 hours was reduced in the pregabalin group by approximately 2.08, 5.36, 10.94, and 19.29mg, respectively [15].

Paech et al. studied the effect of 100mg of pregabalin and found no improvement in postoperative analgesia in short gynecological procedure [16]. While Jokela et al. reported premedication with 150mg pregabalin in gynecological laparoscopic procedure did not require fentanyl consumption. Jokela et al.in another study of theirs found 150mg and 300mg pregabalin effective in postop analgesia for laparoscopic hysterectomy [17-18].

Use of wide spectrum (50-300mg) dose of pregabalin in the above studies and also our pilot study prompted us to compare 75 and 150mg of pregabalin and the rationale behind administrating pregabalin 90 min prior to surgery was that it should attain maximum plasma concentration at the time of surgical stimulation (peak within 30min-2hrs).

Buvanendran et al. studied that 6 hours after a single dose of 300 mg pregabalin orally the CSF pregabalin level is as high as 0.359 μg/mL to reduce CNS hypersensitivity. Evolved pain sensation during movements is enhanced by central neuronal sensitization [19]. The outcome in our study could be most likely due to preoperative pregabalin preventing CNS sensitization.

In our study mild sedation was noted in patients who received 150 mg pregabalin which was both clinically and statistically not significant moreover it helped patient to remain comfortable and facilitated early ambulation postoperatively.

The limitation of our study was that preoperative pain and anxiety scores were not assessed. Pregabalin might alter preoperative pain, mood and anxiety score which maybe correlated to postoperative pain score. Hence multicentric studies in large sample size should be conducted to compare pre and post-operative effects of pregabalin and define benefits and outcome with different dosage in various surgeries. However, in present study oral pretreatment with pregabalin 150mg was found to be more effective than 75mg without any side effects.

Conclusion

In comparison to 75mg, pregabalin pretreatment with 150mg prolongs the duration of sensory and motor blockade in bupivacaine spinal anesthesia.It also delays the time to first request of analgesics and reduces 24 hrs total analgesic requirements postoperatively without any significant side effects. However it does not have any effect on onset of sensory and motor blockade.

To conclude oral pretreatment with pregabalin 150mg could be the optimum dose for patients scheduled for vaginal hysterectomy under spinal anaesthesia.

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