Asian Spine Journal
Clinical Study
Asian Spine J 2019;13(3):441-449 • https://doi.org/10.31616/asj.2018.0121

Perioperative Factors Associated with Severe Pain in Post-Anesthesia Care Unit after Thoracolumbar Spine Surgery: A Retrospective Case-Control Study

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Study Design: A retrospective case-control study.

Purpose: To evaluate the effect of nitrous oxide and anesthetic and operative factors associated with severe pain in the early postoperative period after thoracolumbar spine surgery.

Overview of Literature: Thoracolumbar spine surgery is the most common procedure in spine surgery, and up to 50% of the patients suffer from moderate to severe pain. Nitrous oxide has analgesic, anxiolytic, and anesthetic effects; nevertheless, its benefits for early postoperative pain control and opioid consumption remain to be established.

Methods: The medical records of eligible participants who underwent thoracolumbar spine surgery between July 2016 and February 2017 were reviewed. Enrolment was performed consecutively until reaching 90 patients for the case (severe pain) group (patients with a pain score of ≥7 out of 10 at least once during the post-anesthesia care unit [PACU] admission), and 90 patients for the control (mild-to-moderate pain) group (patients with a pain score of <7 in every PACU assessment). The data collected comprised patient factors, anesthetic factors, surgical factors, PACU pain score, and PACU pain management.

Results: A total of 197 patients underwent thoracolumbar spine surgery with an incidence of early postoperative severe pain of 53.3%. The case-control study revealed no differences in the factors related to pain intensity. A subgroup analysis was performed for failed back surgery syndrome (FBSS), spinal stenosis, and spondylolisthesis. After multivariate analyses, only the age group of 19–65 years and the baseline Oswestry Disability Index (ODI) were found to be significant risk factors for early postoperative severe pain in the PACU (odds ratio [OR], 2.86; 95% confidence interval [CI], 1.32–6.25; OR, 1.03; 95% CI, 1.01–1.05, respectively).

Conclusions: Nitrous oxide, anesthetic agents, and surgical techniques did not affect the early postoperative pain severity. Age under 66 years and the baseline ODI were the significant risk factors for pain intensity during the early postoperative period of the FBSS, spinal stenosis, and spondylolisthesis subgroups.

Keywords: Postoperative pain; Nitrous oxide; Spine surgery; Patient-controlled analgesia; Oswestry Disability Index; Post-anesthesia care unit

Received May 28, 2018; Revised Sep 20, 2018; Accepted Oct 18, 2018

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Asian Spine Journal • pISSN 1976-1902 eISSN 1976-7846 • www.asianspinejournal.org

Introduction

Thoracolumbar spine surgery is one of the most common procedures performed in spine surgery. Up to 50% of the patients suffer from moderate to severe pain after the procedure [1,2], and, in a comparison of 179 surgical procedures, major spine surgery accounted for three of the top six surgeries with postoperative severe pain [3]. In two previous thoracolumbar spine surgery studies, the means of the pain scores by Visual Analog Scale (VAS) score were 7.8 out of 10 [4] and 6.8 out of 10 [5]. This pain score may increase the incidence of delirium [6] and the duration of post-anesthesia care unit (PACU), thereby pushing up the cost of care [7]. Factors identified as possibly affecting the degree of postoperative pain were depression, preoperative pain score, and chronic preoperative opioid use [4,8,9].

Despite the increased awareness about the need for pain management, a 2014 Danish study concluded that pain management after spine surgery was still inadequate [2]. In addition, a survey conducted by a nurse anesthetist in Thailand in 2009 reported that postoperative pain control was undermanaged in most of the Thai hospitals [10]. For example, some hospitals did not record pain scores in the PACU or did not have postoperative pain management guidelines.

In the case of the Siriraj Hospital, for instance, about 300–400 thoracolumbar spinal surgeries are conducted in a year. Up to 50% of the patients in the PACU suffer from severe pain with a 0–10 Numerical Rating Scale (NRS) of ≥7, which needs to be improved. Currently, pain management at the Siriraj Hospital is mainly achieved via the intermittent use of intravenous (IV) opioids. If patients are undergoing extensive spine surgery and are expected to have severe pain after surgery, an IV patient-controlled analgesia (PCA) is administered. Previous studies have shown that IV PCA is a better method of pain relief than intermittent IV opioids. Intrathecal morphine or continuous epidural analgesia provides better pain relief than an IV PCA, although the patients may experience the side effects of nausea, vomiting, and itching [5,11].

Nitrous oxide (N_2O) is an anesthetic gas that has been used for more than 150 years. It has analgesic, anxiolytic, and anesthetic effects when used via the opioid-dependent mechanism and the gamma-aminobutyric acid and N-methyl-D-aspartate receptors [12,13]; moreover, it also decreases pain hypersensitivity in neuropathic pain [13]. Nevertheless, the benefits of using N_2O for the provision of early postoperative pain control and reduced opioid consumption remains to be established [14], and it may increase the risk for postoperative nausea and vomiting. Therefore, the use of N_2O is largely dependent on the preferences of individual anesthesiologists. From our experience together with the data obtained from the routine clinical service at the Siriraj Hospital, the patients who underwent thoracolumbar spine surgery and were exposed to N_2O during general anesthesia appeared to be more likely to develop severe pain (NRS pain ≥7) in the PACU than if not exposed to N_2O. Postoperative pain control in spine patients would be improved if it could be confirmed that there are significant associations between the use of N_2O and the incidence of severe pain in the PACU, and if the other factors that may be associated with pain (such as age, sex, intraoperative opioids, and type of surgery) could be identified.

Materials and Methods

1. Study participants

After this retrospective, case-control study had been approved by the Siriraj Institutional Review Board in May 2017 (Si 270/2017), a review was conducted of the medical records of eligible participants who had been admitted to the PACU, Siriraj Hospital. The recruitment was performed in a consecutive order of PACU admission post July 2017 until 90 patients were identified for each of the two following groups: a severe pain group and a mild-to-moderate pain group. Patients with a pain score of ≥7 out of 10 on at least one occasion during their PACU admission were allocated to the severe-pain group, while those with a pain score of <7 in every assessment were assigned to the mild-to-moderate pain group.

The medical records were scrutinized by two reviewers as follows: a nurse anesthetist and a PACU nurse. During the reviewer training, the study protocol, definitions, and the case record form were explained. Initially, both the reviewers practiced completing the case record forms for 10 cases together. Next, each reviewer independently examined half of the remaining 170 medical records to prepare a form for each case. Each reviewer subsequently checked every 20th form completed by the other reviewer, and 60 of the total 180 case record forms were randomly checked by a third reviewer (an anesthesiologist), following which,

all 180 forms were converted to electronic data for input to PASW SPSS Statistics for Windows ver. 18.0 (SPSS Inc., Chicago, IL, USA). The data comprised the following: age; sex; American Society of Anesthesia (ASA) classification; preoperative pain score; baseline Oswestry Disability Index (ODI); history of chronic pain; surgical diagnosis; type of operation; level of spine surgery; surgical duration; bleeding; intraoperative opioid consumption; use of N_2O and inhalation; local anesthetic infiltration; pain score; duration and degree of opioid consumption in the PACU; and use of PCA.

2. Statistical analysis

The calculation of the sample size was based on the pilot study finding that the incidence of severe pain after thoracolumbar spine surgery at the Siriraj Hospital's PACU was approximately 50%. It was thus assumed that the incidence of early postoperative severe pain after thoracolumbar spine surgery would be greater among patients who received N_2O during general anesthesia than among those who did not. To detect a clinically significant difference with a power of 80%, an alpha error of 0.05 (two-sided) and an odds ratio (OR) of 2.5, each group required 80 patients. To compensate for data that may be found to be missing during the retrospective review, the sample size was adjusted upward to 90 cases for each group.

The data analysis was performed using the independent sample Student *t*-test, the Pearson's chi-square test, and the Mann–Whitney *U*-test, and it employed the program PASW SPSS Statistics for Windows ver. 18.0 (SPSS Inc.). All descriptive data were presented as case (%), mean±standard deviation, and median (interquartile range). Univariate analyses of each factor were performed to calculate the *p*-value, OR, and 95% confidence interval (CI). Multiple logistic regression analysis was performed by choosing the factors with a *p*-value of <0.10; $p<0.05$ was considered to be significant.

Results

Of the 197 patients who underwent thoracolumbar spine

Table 1. Demographic data

Characteristic	Pain intensity in PACU		*p*-value
	Mild-moderate pain (n=90)	Severe pain (n=90)	
Age (yr)	58.6±18.7	58.2±13.7	0.849
Sex (female)	53 (58.9)	53 (58.9)	1.000
Body mass index (kg/m^2)	25.2±5.36	24.6±4.03	0.423
American Society of Anesthesia status			0.106
I	8 (8.9)	16 (17.8)	
II	56 (62.2)	57 (63.3)	
III	26 (28.9)	17 (18.9)	
Preoperative pain score (Visual Analog Scale)	4.1±2.8	4.7±2.5	0.105
Baseline Oswestry Disability Index (missing 19 cases)	43.9±20.5	49.4±17.8	0.070
Chronic pain	45 (50.0)	47 (52.2)	0.882
Surgical diagnosis			0.699
Failed back surgery syndrome	8 (8.9)	9 (10.0)	
Adolescent idiopathic scoliosis	5 (5.6)	1 (1.1)	
Spinal stenosis	38 (42.2)	41 (45.6)	
Spondylolisthesis	25 (27.8)	27 (30.0)	
Fracture/cancer/infection	11 (12.2)	9 (10.0)	
Others	3 (3.3)	3 (3.3)	
Numerical Rating Scale in PACU	0.59±1.3	8.5±1.2	<0.001

Values are presented as mean±standard deviation or number (%).
PACU, post-anesthetic care unit.

surgery during July 2016–February 2017, the incidence of early postoperative severe pain was 53.3%. The medical records were reviewed to identify 180 cases for inclusion in the study. Three cases were dropped completely because important data were missing. Ninety cases were subsequently selected for the mild-to-moderate pain group, and 90 others for the severe-pain group. Both groups were similar in terms of age, sex, body mass index, ASA status, preoperative pain score, baseline ODI, history of chronic pain, and surgical diagnosis (Table 1). Only one patient was diagnosed with depression, and three others were on amitriptyline or nortriptyline. One patient was recorded taking an antiepileptic drug.

N_2O was used in 59 cases, which included 29 out of the 90 cases (32.2%) in the mild-to-moderate pain group and 30 out of the 90 cases (33.3%) in the severe-pain group (p=1.00). The prevalence of using N_2O was not statistically different for the early postoperative mild-to-moderate and severe-pain patient groups.

Univariable and multivariable analyses were performed by selecting the factors whose p-values were <0.10, namely, the age-group, baseline ODI, surgical duration, blood loss, total morphine consumption, and IV PCA–opioid use. Only the IV PCA–opioid use was found to be a marginally significant preventive factor for early postoperative severe pain in the PACU (p=0.05; OR, 0.05; 95% CI, 0.24–1.00).

To understand the subject better, a post hoc analysis was performed in the subgroup of patients whose diagnoses suggested that they were prone to high postoperative pain scores. These diagnoses were failed back surgery syndrome (FBSS), spinal stenosis, and spondylolisthesis (Table 2). They also formed the majority of patients in our setting (n=148).

The proportion of patients who experienced severe pain in the PACU tended to be higher in the 19–65-year age group than in the >65-year age group (p=0.056). The mean baseline ODI was significantly higher for the severe-pain group than for the mild-to-moderate pain group, with scores of 49.7±16.2 and 42.2±20.6, respectively (p=0.018). The mean surgical duration was significantly longer for the mild-to-moderate pain group (242±108 minutes) than for the severe-pain group (204±76 minutes, p=0.018). The intraoperative blood loss was greater in the mild-to-moderate pain group than in the severe-pain group, with median (interquartile range) blood losses of 500 mL (range, 250–800 mL) and 400 mL (range, 175–700 mL), respectively (p=0.055). The intraoperative morphine equivalences did not differ between the two groups. More patients in the mild-to-moderate pain group received IV PCA–opioids than in the severe-pain group, with 25 cases (35.2%) versus 15 cases (19.5%), respectively, and p=0.031.

The multiple logistic regression analysis was performed by selecting the factors whose p-values were <0.10, namely the age group, baseline ODI, surgical duration, blood loss, and IV PCA–opioid use (Table 3). Only the 19–65-year age group and baseline ODI were found to be significant risk factors for early postoperative severe pain in PACU. The age group 19–65 years had a p=0.007 and an adjusted OR of 2.86 (95% CI, 1.32–6.25). The baseline ODI had p=0.004 and an adjusted OR of 1.03 (95% CI, 1.01–1.05).

The postoperative results are shown in Table 4. The PACU duration for the severe-pain group (86.2±27.3 minutes) was longer than that for the mild-to-moderate pain group (78.4±25.4 minutes, p=0.048). Morphine consumption during PACU admission was also higher for the severe-pain group than for the mild-to-moderate pain group (the median consumptions were 4 and 0 mg, respectively; p<0.001). Moreover, the frequency of opioids received in the PACU was higher for the severe-pain group (2.5 times) than for the mild-to-moderate group (0 times, p<0.001).

In addition, the pain intensity during the 24-hour period after surgery was higher for the severe-pain group. The median of the highest VAS pain score at 0–6 hours was 5 for the severe-pain group as compared with 4 for the mild-to-moderate group (p=0.001). At 7–24 hours, the scores for the two groups were 4 and 2, respectively (p=0.002).

Furthermore, the incidences of pain in the severe-pain and mild-to-moderate groups at 0–6 hours were 33 (37.1%) and 17 (19.8%), respectively; at 7–24 hours, the numbers halved to 15 (16.9%) and 8 (9.1%), respectively.

Discussion

Pain is one of the major complications after spine surgery. The cutoff points for mild, moderate, and severe pain in pain assessment are still unclear, and they are dependent on the patients' pain-thresholds [15,16]. To highlight the problem during the postoperative spine surgery period, the definition of severe pain employed in this study was an NRS of ≥7, which provided an explicit cutoff point. The

Table 2. Subgroup analysis factors related to postoperative pain intensity for the group of diagnoses related to high postoperative pain scores

Variable	Pain intensity in post-anesthesia care unit		*p*-value
	Mild-moderate pain (n=71)	Severe pain (n=77)	
Age group (yr)			0.056
0–18	0	0	
19–65	38 (53.5)	53 (68.8)	
>65	33 (46.5)	24 (31.2)	
American Society of Anesthesia status			0.223
I	6 (8.5)	10 (13.0)	
II	44 (62.0)	53 (68.8)	
III	21 (29.6)	14 (18.2)	
Sex (female)	40 (56.3)	47 (61.0)	0.562
Preoperative pain score (Visual Analog Scale)	4.4±2.6	4.7±2.5	0.441
Baseline Oswestry Disability Index unit (missing 8 cases)	42.2±20.6	49.7±16.2	0.018*
Chronic pain	37 (52.1)	40 (51.9)	0.984
Level of laminectomy			0.574
0	11 (15.5)	13 (16.9)	
1–2	33 (46.5)	41 (53.2)	
>2	27 (38.0)	23 (29.9)	
Level of posterior instrument			0.657
0	5 (7.0)	10 (13.0)	
1–2	27 (38.0)	29 (37.7)	
3–5	34 (47.9)	34 (44.2)	
>5	5 (7.0)	4 (5.2)	
Level of interbody fusion			0.360
0	25 (35.2)	36 (46.8)	
1	32 (45.1)	29 (37.7)	
>2	14 (19.7)	12 (15.6)	
Type of interbody fusion			0.234
Posterior lumbar interbody fusion	20 (28.2)	12 (15.6)	
Transforaminal lumbar interbody fusion	15 (21.1)	19 (24.7)	
ALIF/XLIF/OLIF[a]	11 (15.5)	10 (13.0)	
None	25 (35.2)	36 (46.8)	
Surgical duration (min)	242±108	204±76	0.018*
Blood loss (mL)	500 (250–800)	400 (175–700)	0.055
Nitrous oxide	23 (32.4)	28 (36.4)	0.612
Minimum alveolar concentration of inhalation	0.66±0.15	0.68±0.16	0.272
Morphine equivalence (mcg/kg/min)	1.04±0.57	1.89±0.61	0.167
Local infiltration	30 (42.3)	34 (44.2)	0.815
Patient-controlled analgesia (opioids)	25 (35.2)	15 (19.5)	0.031*

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
*p<0.05 indicates statistical significance. [a]Anterior lumbar interbody fusion/extreme lateral interbody fusion/oblique lumbar interbody fusion.

Table 3. Factors influencing severe pain during early postoperative period after multivariable analysis

Variable	*p*-value	Adjusted odd ratio (95% confidence interval)
Age (19–65 yr)	0.007*	2.86 (1.32–6.25)
Baseline Oswestry Disability Index unit	0.004*	1.03 (1.01–1.05)
Surgical duration (min)	0.236	0.99 (0.99–1.00)
Blood loss (mL)	0.797	1.00 (1.00–1.00)
Patient-controlled analgesia (opioids)	0.059	0.44 (0.19–1.03)

*p<0.05 indicates statistical significance.

Table 4. Postoperative results

Variable	Pain intensity in PACU		*p*-value
	Mild-moderate pain (n=90)	Severe pain (n=90)	
PACU duration (min)	78.4±25.4	86.2±27.3	0.048*
Morphine in PACU (mg)	0 (0–0)	4 (2–6)	<0.001*
Frequency of opioids received (times)	0 (0–0)	2.5 (1.75–3)	<0.001*
Maximum NRS at 0–6 hr	4 (0–6)	5 (3–7)	0.002*
Maximum NRS at 7–24 hr	2 (0–5)	4 (2–5)	0.006*
Severe pain at 0–6 hr (NRS)	17 (19.8)	33 (37.1)	0.009*
Severe pain at 7–24 hr (NRS)	8 (9.1)	15 (16.9)	0.094

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
PACU, post-anesthesia care unit; NRS, Numerical Rating Scale.
*p<0.05 indicates statistical significance.

incidence of severe pain after thoracolumbar spine surgery in this study was 53.3%, which is a matter of concern.

The results of the previously mentioned pilot study suggested that N_2O may be associated with the development of severe pain during the early postoperative period. Nevertheless, the current study found no correlation between the intraoperative use of N_2O and the early-postoperative severe pain. N_2O was used as an adjuvant anesthetic gas in 59 (32.78%) of the patients undergoing thoracolumbar spine surgery. Although the concentration of inhaled anesthetic was noticeably reduced with statistical significance in the N_2O subgroup (minimum alveolar concentration of inhalation was 0.61±0.16 versus 0.72±0.14 in the non-N_2O subgroup; p<0.001), the use of N_2O did not yield any clinical significance. Furthermore, a decrement in the intraoperative total opioid doses was not observed in the current study. These results suggest that the advantages of N_2O for spine surgery are still indistinct, and, therefore, its use is still debatable. Consequently, before adopting N_2O for use in clinical practice, it is important to weigh the perceived benefits against the risks.

The disadvantages of employing N_2O for spine surgery include the risk of pneumocephalus or air entrapment in the epidural space, which may result in subsequent neurological deficits in patients whose dura is torn or intentionally opened [17,18]. Moreover, the use of N_2O increases the risk for postoperative nausea and vomiting. However, postoperative cognitive dysfunction and cardiovascular complications are not associated with N_2O, according to the study of Myles et al. [19].

The surgical diagnoses which related to severe pain were FBSS, spinal stenosis, and spondylolisthesis. The diagnoses of adolescent idiopathic scoliosis, fracture, cancer, infection, and the rest seemed to have lower pain scores during the early postoperative period. However, surgical diagnosis was not noted to be a risk factor for postoperative severe pain in the PACU, as demonstrated in Table 1. From the subgroup analysis of the diagnoses related to high pain scores, it was found that a patient aged 19–65 years and/or with a high baseline ODI score was at significant risk for early postoperative severe pain in the PACU.

Depression, the preoperative pain score, and chronic

preoperative opioid use had been reported as important risk factors for postoperative pain and other complications [4,8,9]. However, the analysis of the patients' psychological profiles or mental states was not routine at our institute. The preoperative spinal surgery evaluation protocol involved the preoperative pain (VAS) and baseline ODI scores, except for patients with diagnosed scoliosis. According to a medical record review, only four patients were taking antidepressant medications (amitriptyline or nortriptyline) and 92 patients (51%) were taking gabapentin, pregabalin, or tramadol, presumably due to their chronic pain. No prescriptions for preoperative strong opioids were noted. Because depression screening has been an ongoing issue in Thailand, our study had a limited ability to explore the factors related to mental status. Nonetheless, this study found that a high baseline ODI score may increase the risk of severe pain after thoracolumbar spine surgery, albeit further studies are needed to establish the relevant cutoff point. Unlike in previous studies, the preoperative pain score failed to be a statistically significant risk factor in our study. We thus propose that a single preoperative pain score cannot be a reliable assessment for spinal surgery patients.

In this study, the postoperative use of IV PCA seemed to be a preventive factor that improved the pain outcomes during the early postoperative period, specifically until the end of the first 24 hours after surgery (adjusted OR, 0.05). However, IV PCA was not a significant preventive factor in the subgroup of FBSS, spinal stenosis, and spondylolisthesis. Patients who suffered from severe pain showed a tendency toward a longer PACU stay since having adequately controlled pain is mandatory prior to PACU discharge (Table 4). Although the standardized postoperative pain protocol is presently inconclusive for major spine surgeries, IV PCA–opioids seem to be are a promising option for postoperative pain control with minimal adverse effects. Other satisfactory alternatives for pain control after major spine surgery are a single-shot or continuous epidural analgesia and intrathecal morphine. These techniques can reduce the IV opioid consumption; nonetheless, several studies have reported that pruritus and postoperative nausea vomiting were more common with these alternatives [5,20,21].

Several published studies have suggested that preoperative pain intensity is a major predictor for the occurrence of postoperative severe pain [4,22]. An individual postoperative pain control regimen can possibly be established with the continuous evaluation of a patient's perioperative pain intensity and perception. The utilization of multiphasic and multimodal analgesia is strongly recommended [23,24]. The current study cannot substantiate the result of preoperative pain intensity toward the development of severe pain because a systematic evaluation of the preoperative pain score is insufficient. Although the preoperative use of chronic pain medications may be suggestive, the duration of the pain is still lacking.

Since the development of postoperative intense pain after major spine surgery is difficult to control, the establishment of a postoperative pain control protocol for major spine surgery is crucial to relieve postoperative pain to the maximum possible extent. If the protocol was available, the patients would be able to promptly recover from surgery, and the postoperative complications would be significantly reduced. Enhanced recovery after surgery should also be advocated with a multidisciplinary team—namely surgeons, anesthesiologists, nurses, and physiotherapists—who should be present throughout the perioperative period to help achieve the best outcomes for patients undergoing major spine surgeries [25-28].

Since the study was designed as a retrospective chart review, some data were not completely recorded, such as the psychological profile, the diagnosis of chronic pain, the preoperative pain intensity, the local anesthetic or ketorolac infiltration by the surgeons, and the delivered dose of opioids via a PCA machine. Our findings are also subject to bias from unmeasured confounders such as surgeons, anesthesiologists, and PACU nurses who assessed the pain intensity.

Conclusions

The anesthetic regimen of general anesthesia for thoracolumbar spine surgery and surgical techniques did not affect the early postoperative severe pain. An age under 66 years and a high baseline ODI were the significant risk factors for pain intensity during the early postoperative period in cases of FBSS, spinal stenosis, and spondylolisthesis.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

The authors are indebted to the Siriraj R2R team members for consultation on this paper; Miss Julaporn Pooliam for assistance with the methodology; Miss Chusana Rungjindamai for her invaluable support with administrative work; and Mr David Park for thoroughly copy editing the manuscript.

Funding

This research project was supported by Siriraj Research Development Fund (managed by Routine to Research: R2R), Faculty of Medicine Siriraj Hospital, Mahidol University (grant no., 17AS00024/003/17).

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Conception and design: PR, TS, BS; acquisition and data: PR, TS; analysis and interpretation of data: PR, TS, BS; drafting of the manuscript: BS; critical revision of the manuscript for important intellectual content: AN, BS; statistical analysis: AN, BS; supervision: AN, BS; obtaining funding: BS; and administrative, technical, or material support: BS

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