



Intrathecal Morphine Is Associated with Less Delirium Following Hip Fracture Surgery: A Register Study

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Abstract

Background: Delirium is a common complication after proximal femoral fracture surgery, with pain and opioid consumption as the contributing factors. The administration of intrathecal morphine may decrease these factors postoperatively and potentially reduce delirium.

Objectives: This research aimed to study the association between the use of intrathecal morphine and the occurrence of delirium.

Methods: A retrospective analysis of a prospective register kept in a non-academic hospital in the Netherlands was performed. The register contained data of all patients with proximal femur fractures that were surgically treated with osteosynthesis or prosthesis. Patients receiving spinal anesthesia (SA group) were compared with patients receiving spinal anesthesia with the addition of intrathecal morphine (SIM group). The administration of either SA or SIM was based on the preference of the anesthesiologist. The primary outcome was the incidence of delirium, as defined by the DSM-V classification. The follow-up lasted until hospital discharge. Both univariate and multivariate analyses were performed.

Results: The SA group consisted of 451 patients, and the SIM group included 34 patients. Delirium occurred in 19.7% in the SA group versus 5.9% in the SIM group ($P = 0.046$). This association remained significant after correction in multivariate analysis (OR of delirium in the SA group, 95% CI: 1.062 - 21.006, $P = 0.041$). Additionally, multivariate analysis revealed that age, gender, preoperative cognitive impairment, and fracture treatment (osteosynthesis or prosthesis) were independently associated with delirium.

Conclusions: This retrospective study found an independent association between the use of intrathecal morphine and a lower incidence of delirium. This clinically relevant decrease in delirium should be studied in a prospective randomized study.

Keywords: Spinal Anesthesia, Morphine, Spinal Injections, Delirium, Femoral Fractures

1. Background

Delirium is one of the most prevalent perioperative complications of proximal femoral fracture surgery (1). It is associated with an increased mortality, prolonged admission time, and impaired functional recovery, and is prognostic for cognitive impairments and dementia (2). Among the factors influencing the incidence of delirium during admission are pain and systemic opioid use (3, 4). Both pain and systemic opioid use decrease with the administration of intrathecal morphine, which provides adequate analgesia for approximately 24 to 48 hours (5). Consequently, intrathecal morphine could potentially reduce the prevalence of postoperative delirium in proximal femoral fracture patients.

In contrast, the Royal College of Physicians recommends against the routine use of intrathecal morphine due to the risk of side effects, including postoperative confusion (6). This claim seems questionable since only one study has investigated intrathecal morphine in proximal femoral fracture patients, which detected no difference in complications, although it was underpowered for this outcome measure (7, 8). Furthermore, studies involving intrathecal morphine in older patients undergoing elective hip surgery did not find an increased risk of postoperative delirium (9-11).

2. Objectives

The goal of this study was to investigate if the administration of intrathecal morphine is associated with a lower incidence of delirium when compared to spinal anesthesia without intrathecal morphine in patients treated surgically for a proximal femoral fracture. All patients admitted with a proximal femoral fracture were registered in a prospective database in the study hospital. A minority of the anesthesiologists added morphine to the intrathecal bupivacaine for spinal anesthesia, which made it possible to allocate patients to different groups. A retrospective analysis of that database was performed as a hypothesis-generating study.

3. Methods

A retrospective analysis was performed with data that were routinely and prospectively registered in a database. The database was not specifically designed for anesthesia-related influences on delirium. Data were registered simultaneously with the clinical registrations during admission by clinicians as part of routine care for all patients admitted with a proximal femoral fracture to the “Hip Fracture Centre” of the Haaglanden Medical Centre Bronovo in The Hague, the Netherlands. All treatment aspects and data registrations presented in this study are documented in the local care pathway protocol. All data were handled in agreement with the “code of conduct for health research” of the Council of the Federation of Medical Scientific Societies. The personal data were handled according to the Dutch Personal Data Protection Act. The methodology of data collection and any subsequent observational studies was approved by the institutional Medical Research Ethics Committee (METC Southwest Holland; protocol number: 18-029) without the need for individual patient consent due to the observational nature of the study.

3.1. Patients

Data were used from all patients surgically treated under intrathecal anesthesia between 19-12-2016 and 14-01-2019. The patients were divided into two groups, based on the type of anesthesia, including spinal anesthesia (SA) or spinal anesthesia with intrathecal morphine (SIM). The choice of administration of intrathecal morphine was only at the discretion of the treating anesthesiologist.

3.2. Methods

After the radiological diagnosis of a proximal femoral fracture, patients were admitted to the surgical ward. The EKG and laboratory investigations were performed, and additional preoperative investigations initiated when necessary. Screening for cognitive impairments was routinely performed using the Six-item Cognitive Impairment test (6CIT) for all older patients (age ≥ 70) without a known diagnosis of dementia or other cognitive impairments (12). The 6CIT was designed to assess the global cognitive status in dementia. Developed in the 1980s as an abbreviated version of the 26-item Blessed Information-Memory Concentration scale, the 6CIT is an internationally used, well-validated screening tool. It was designed principally for use in primary care but has also found application in secondary care settings.

The patients' delirium risk was assessed using the (Dutch) National Safety Management System (VMS) theme “Frail Elderly” by the ward nurses (13). Patients with elevated delirium risk and patients with a clinical suspicion of delirium were screened three times daily by trained nurses using the Delirium Observation Screening scale (DOSS) (14). The DOSS is an observation scale consisting of 13 items (see Appendix 1 in Supplementary File). It is a validated, nurse-led screening tool that can be completed within five minutes. The DOSS score varies between 0 and 13, which is correlated with the severity of delirium (15). When delirium was suspected (DOSS score > 3), a psychiatrist was consulted to diagnose delirium using the DSM-V criteria.

Perioperative pain management consisted of paracetamol 1000 mg q.i.d., diclofenac 50 mg t.i.d. and subcutaneous piritramide 5 - 10 mg when requested. Regional nerve blocks were not routinely administered in this cohort.

All patients received a type of anesthesia depending on the preference of the patient and the attending anesthesiologist. Only severe aortic valve stenosis (aortic valve area $< 0.8 \text{ cm}^2$), pulmonary hypertension (mean Pulmonary Arterial Pressure $> 50 \text{ mmHg}$), or coagulation disorders (PT $> 1.8 \text{ INR}$, use of clopidogrel) were absolute contraindications for spinal anesthesia. Spinal anesthesia was performed with bupivacaine 5 mg/mL, and the dose was at the discretion of the anesthesiologist. Morphine was added to the intrathecal mixture based on individual preferences by the anesthesiologists. Preservative-free morphine was diluted from 10 mg/ml to 100 mcg/mL by a double dilution technique. To administer the intrathecal injection, patients were sedated with propofol/esketamine or propofol/alfentanil for positioning, depending on the preference

of the anesthesiologist. It is common practice in our institution to sedate the patient with spinal anesthesia with continuous infusion of propofol during surgery. Propofol was targeted at a BIS value > 45 (Bispectral Index System, Medtronic, Minneapolis, MN, USA) or a maximum of 2.5 mg/kg/h. Patients without intrathecal morphine received 5-10 mg piritramide subcutaneously in the recovery ward as a loading dose. Further intravenous titration of piritramide with increments of 2.5 mg was available on the recovery ward for all patients. After surgery, pain management was resumed as previously described.

Patients recovered on a special 10-bed division of the surgical ward dedicated to proximal femoral fracture patients. Routine delirium preventative measures for patients with elevated risk consisted of providing a clearly visible clock, the immediate appliance of hearing and visual aids, stimulation of normal day-night rhythm and providing familiar items, and the possibility of rooming-in of family members. Patients were visited daily during the rounds by the ward doctor, a surgeon, and a senior nurse.

Patients were discharged only if they were hemodynamically and respiratory stable, the functionality corresponded with the discharge location, there were no signs of complications for which diagnostics or treatments were indicated (e.g., infection, electrolyte disorders), and the pain was controlled with oral medication.

3.3. Methods of Assessment

The primary outcome was defined as the occurrence of delirium during admission. The secondary outcomes were pain, length of hospital stay, and complications, including infection, respiratory failure, and mortality. The duration of follow-up was set to the length of hospital stay until discharge since no pharmacotherapeutic effect of intrathecal morphine is expected beyond this timepoint. The missing data were not imputed or replaced.

Definitions of the complications, treatment aspects, and data collection have been presented previously in more detail by van der Sijp et al. (16). Applicable definitions for this study are as follows:

Cognitive impairment was defined as previously diagnosed dementia, or an abnormal 6CIT score (≤ 11) used to screen for cognitive impairments during admission in the ED (12).

The pain was scored three times daily during admission on a Numeric Rating scale (NRS) with the range of 0-10. The highest postoperative pain score for each patient was registered.

Systemic infections were pooled and scored when a patient had a temperature ≥ 38.5 degrees of celsius, elevated C-reactive protein (CRP) levels (> 10 mg/L), or a white blood cell count $> 12.5 \times 10^6$ /mL, a clinically susceptible site of infection, and (antibiotic) therapy use.

Respiratory insufficiency was defined as a need for supplemental oxygen or intubation after surgery.

All patients with elevated DOS scores were evaluated by a physician. Delirium was diagnosed according to the DSM-V criteria (17).

3.4. Statistical Analysis

Patients were allocated according to their method of anesthesia, as described previously. Categorical variables are presented as frequency (percentage) and were compared using the chi-square test or Fisher's exact test if the data were insufficiently large (expected cell counts ≤ 5). Continuous data were presented as median with the interquartile range (IQR) and compared using the independent sample *t*-test and the Mann-Whitney U-test, depending on the data distribution. A multiple linear regression analysis was used to study the effect size of the anesthesia type (intrathecal anesthesia either with or without morphine) concerning the incidence of delirium during admission. The multivariate analysis was used to adjust for suspected confounding factors, and factors included for multivariate analysis were suspected confounding factors and factors identified in the univariate analysis with a P value of < 0.10 . The one-in-ten rule was applied to limit the number of adjusting variates. A P value of 0.05 was considered statistically significant for all other outcomes. All statistical analyses were performed using IBM SPSS version 25.0 software (IBM, Armonk, New York).

4. Results

A total of 1,028 patients were admitted to the study hospital with a proximal femoral fracture between 19 December 2016 and 14 January 2019. From these, 999 (97.1%) patients were treated surgically. However, 514 (50.7%) patients who were surgically treated received general anesthesia and were consequently not included in the study. Of the 485 remaining patients, 451 (93.0%) were treated with spinal anesthesia and 34 (7.0%) with spinal anesthesia with intrathecal morphine. The dose of intrathecal morphine ranged between 100 μ g and 150 μ g. The baseline characteristics were comparable (Table 1). Of the treatment aspects, only the operating time (skin-to-skin) differed significantly

Table 1. Baseline Characteristics^a

	SA (N = 451) (93.0%)	SIM (N = 34) (7.0%)	P Value
Age, y	83 (75 - 90)	84 (75 - 89)	0.903
Sex (% female)	313 (69.4)	22 (64.7)	0.568
BMI, kg/m ²	23.3 (21.2 - 25.5)	24.0 (21.3 - 27.6)	0.243
ASA classification			
I	31 (7.0)	0 (0.0)	
II	175 (39.6)	11 (32.4)	
III	217 (49.1)	20 (58.8)	
IV	19 (4.3)	3 (8.8)	0.187
Katz-ADL			
0 - 2	323 (73.4)	26 (76.5)	
3 - 4	62 (14.1)	5 (14.7)	
5 - 6	55 (12.5)	3 (8.8)	0.820
Living situation			
Independent	272 (60.3)	19 (55.9)	
Homecare or residential home	86 (19.1)	10 (29.4)	
Nursing home	82 (18.2)	5 (14.7)	
Other	11 (2.4)	0 (0.0)	0.415
Cognitive impairment	159 (36.1)	8 (23.5)	0.138
Fracture type			
FNF	266 (59.0)	22 (64.7)	
PFF	174 (38.6)	12 (35.3)	
Other	11 (2.4)	0 (0.0)	0.579
Time to surgery, h	21 (14 - 28)	23 (15.5 - 31.5)	0.472
Preoperative nerve block	25 (9.8)	5 (18.5)	0.183 ^a
Fracture treatment			
Prosthesis	201 (44.5)	20 (58.8)	
Osteosynthesis	251 (55.5)	14 (41.2)	0.105
Operating time, min	52 (40 - 68)	69 (55 - 79)	< 0.001 ^b

Abbreviations: FNF, femoral neck fracture; h, hours; min, minutes; Katz-ADL, Katz Index of Independence in activities of daily living; A scale from 0 to 6 indicating the level of independence; PFF, pertrochanteric femoral fracture; SA, spinal anesthesia; SD, standard deviation; SIM, spinal anesthesia with intrathecal morphine.

^aFisher's exact test (two-tailed).

^bIt indicate statistical significance.

between the groups (SA: 52 min (10 - 164) vs. SIM: 69 min (27 - 129), $P < 0.001$).

No statistically significant differences were observed in the clinical outcomes (Table 2). From all studied perioperative complications, only the incidence of delirium varied significantly between the two study groups (19.7% vs. 5.9%, $P = 0.047$). One patient in the SIM group died because of persistent hypotension after treatment with a prosthesis, clinically attributed to the use of cement intraoperatively.

Multivariate analysis was performed to exclude factors

confounding the association between delirium and the type of intrathecal anesthesia. Potential confounding factors identified in the univariate analysis were “operating time” and “treatment type”. Suspected confounding factors were “age”, “gender”, “ASA classification”, and “cognitive impairment”. The analysis affirmed an association between intrathecal morphine use and a lower incidence of delirium (OR: 4.723, 95% CI: 1.062 - 21.006; $P = 0.042$) (Table 3).

Table 2. Clinical Outcomes^a

	SA (N = 451) (93.0%)	SIM (N = 34) (7.0%)	P Value
Admission time, d	4 (3 - 7)	5 (4 - 7)	0.273
Reason for prolonged admission			
Comorbidities	15 (7.3)	1 (5.0)	
Complications	54 (26.3)	8 (40.0)	
Logistics	116 (56.6)	11 (55.0)	
Other	3 (1.5)	0 (0.0)	0.504
Highest postoperative pain score (NRS)	4 (3 - 6)	3 (2 - 6)	0.170
Opioid use at discharge	114 (25.2)	7 (20.6)	0.547
Delirium	89 (19.7)	2 (5.9)	0.047 ^a
POWI			
Superficial	2 (0.4)	0 (0.0)	1.000 ^b
Deep	0 (0.0)	0 (0.0)	-
Systemic infections	44 (9.7)	2 (5.9)	0.760
Renal failure	17 (3.8)	1 (2.9)	1.000 ^b
Myocardial infarction	1 (0.2)	1 (2.9)	0.135 ^b
Stroke	2 (0.4)	0 (0.0)	1.000 ^b
Respiratory insufficiency	11 (2.4)	0 (0.0)	1.000 ^b
In-hospital mortality	7 (1.5)	1 (2.9)	0.443 ^b

Abbreviations: DOS, Delirium Observational scale; MI, myocardial infarction; NRS, Numeric Rating scale; POWI, postoperative wound infection.

^aIt indicate statistical significance.

^bFisher's exact test (2-sided).

5. Discussion

This hypothesis-generating retrospective study showed that the use of intrathecal morphine for postoperative pain in patients with proximal femoral fractures was independently associated with a lower incidence of postoperative delirium. This association remained significant after correction for age, gender, ASA classification, pre-existing cognitive impairment, duration of surgery, and fracture treatment.

The pathogenesis of delirium is not fully elucidated, although multiple factors are associated with its occurrence (18). The well-known risk factors are age, gender, ASA classification, premorbid cognitive impairment, fracture treatment, pain, and medications, including opioids (19, 20). The current study identified previously known risk factors for delirium, which demonstrates the reproducibility of this cohort. Furthermore, the incidence of delirium is in line with the findings of other studies (21).

The study effects are attributed to intrathecal morphine, although the lack of a subcutaneous loading dose of piritramide in the recovery room could be a cause, as well. These two factors were the only differences in the analgesic

regimen between the SA and SIM groups. Even though the administration of a loading dose is controversial, in our practice, it is common to administer some opioids because pain may contribute to the development of delirium, as well. This practice is supported by the fact that emergency hip fracture surgery is so painful that patients need postoperative opioids (22). This would imply that leaving out a loading dose would not decrease opioid consumption because patients would require opioids anyway. In addition, paracetamol and diclofenac were used as basal analgesic regimens because of the opioid-sparing effects. The study effect persisted despite the use of this basal analgesic regimen.

To date, only one study has prospectively investigated the use of intrathecal morphine for postoperative pain in patients undergoing surgery for proximal femoral fractures, but the occurrence of delirium was not measured (8). Since delirium is a predominant complication after surgical treatment of proximal femoral fractures in elderly patients with significant consequences, a possible reduction through the use of intrathecal morphine may be clinically relevant and should be studied prospectively.

Table 3. Multivariate Analysis (Logistic Regression) for Delirium

	Adjusted OR	95% CI	P Value
Age, y	1.050	1.016 - 1.085	0.003
Sex			
Male	Ref.		
Female	0.455	0.261 - 0.791	0.005
ASA classification			
I	Ref.		
II	> 999	0.000 - NA	0.998
III	> 999	0.000 - NA	0.998
IV	> 999	0.000 - NA	0.998
Cognitive impairment			
No	Ref.		
Yes	1.950	1.135 - 3.350	0.016 ^a
Operating time, min	1.002	0.991 - 1.013	
Intrathecal anesthesia			
SIM	Ref.		
SA	4.723	1.062 - 21.006	0.041 ^a
Fracture treatment			
Prosthesis	Ref.		
Osteosynthesis	0.476	0.278 - 0.815	0.007 ^a

Abbreviations: CI, confidence interval (of OR); min, minutes; NA, not available; OR, Odds Ratio; Ref., reference; SA, spinal anesthesia; SIM, spinal anesthesia with intrathecal morphine; y, years.

^aIt indicate statistical significance.

A possible mechanism by which intrathecal morphine reduces postoperative delirium is likely to involve reduced postoperative pain and reduced systemic opioid administration (23). Both factors are associated with delirium and are reduced by the use of intrathecal morphine (5, 20). The systemic effects of opioids are possibly involved in delirium, and due to its hydrophilic nature, intrathecal morphine exerts a selective spinal effect with few systemic effects (24).

Continuous regional or neuraxial anesthesia might be an alternative to reduce postoperative pain scores and systemic opioid consumption and, thus, could potentially reduce delirium, as well (25). However, these analgesic methods may cause a motor block, which might hamper mobilization and rehabilitation through early postoperative physiotherapy, making it less attractive as a postoperative analgesic. Additionally, peripheral nerve blocks might not completely block the innervation of the proximal femur, which limits the analgesic effects in some patients (26-28). These disadvantages do not occur with intrathecal mor-

phine, since this produces an analgesic effect at a spinal level and does not inhibit motoric function. Furthermore, the prolonged analgesic effect of continuous regional techniques relies on the position of a catheter, while intrathecal morphine can be administered with a single-shot technique.

Several important limitations inherent in our study design should be considered. First, due to the observational nature of this study, no causative effect can be concluded. Second, a vast majority of patients (93.0%) were treated without intrathecal morphine due to an uneven division of the anesthesiologists based on their personal preference and professional experience. The third limitation, as mentioned previously, is that the study effect could be attributed to the lack of a piritramide loading dose, rather than the administration of intrathecal morphine in the SIM group. As discussed, we believe that the loading dose would be required anyway, making this theory unlikely. Fourth, other anesthesia- or anesthesiologist-related treatment aspects, which may have differed between the minority group of anesthesiologists using intrathecal morphine and other anesthesiologists, may have contributed to the observed study outcomes. As this study was based on a routine prospective register, variables available for study purposes were limited. Additional study outcomes of interest would include the actual postoperative opioid consumption of patients, daily pain scores during admission, sedation scores, the time and extent of enteral nutrition after surgery, and the time and extent of the first mobilization after surgery. Because these were unavailable, the hypothesized mechanism for the reduced incidence of delirium could not be tested in this study. Fifth, the number of preoperative nerve blocks was low in both groups. These nerve blocks could decrease the use of preoperative opioids and pain scores, which might affect delirium, as well. Finally, the risk of bias was considerable, e.g., because nurses were more reluctant to administer opioids in patients with intrathecal morphine.

5.1. Conclusions

In conclusion, this retrospective study generated a hypothesis that the use of intrathecal morphine might reduce the incidence of delirium. Lower pain scores and less opioid consumption in the postoperative period is the proposed mechanism that causes less delirium. This result urges for further explorations of this analgesic method in the occurrence of delirium in a randomized study since this study carries a high risk of bias.

Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

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Footnotes

Authors' Contribution: Study concept and design: MVK. Acquisition of data: MvdS and AHPN. Analysis and interpretation of data: MVK, MvdS, AHPN, and RJS. Drafting of the manuscript: MVK and MvdS. Critical revision of the manuscript for important intellectual content: AHPN and RJS. Statistical analysis: MvdS. Study supervision: AHPN and RJS.

Conflict of Interests: None of the authors has any conflicts of interest to declare.

Ethical Approval: All data were handled in agreement with the "code of conduct for health research" of the Council of the Federation of Medical Scientific Societies. Personal data were handled according to the Dutch Personal Data Protection Act. The methodology of the data collection and any subsequent observational studies was approved by the Institutional Medical Research Ethics Committee (METC Southwest Holland; protocol number 18-029).

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