Intrathecal morphine is associated with less delirium following hip fracture surgery; a register study

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Research article

Keywords: intrathecal morphine, delirium, hip fracture surgery

Posted Date: August 2nd, 2019

DOI: https://doi.org/10.21203/rs.2.12306/v1

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Version of Record: A version of this preprint was published at Anesthesiology and Pain Medicine on August 26th, 2020. See the published version at https://doi.org/10.5812/aapm.106076.
Abstract

Purpose Delirium is a common complication after proximal femoral fracture surgery and contributing factors are pain and opioid consumption. The administration of intrathecal morphine may decrease these factors postoperatively and potentially decrease delirium. The aim of this research is to study the association between the use of intrathecal morphine and the occurrence of delirium. Methods A retrospective analysis of a 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 with local anesthetics (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. Primary outcome was the incidence of delirium, as defined by the DSM-V classification. Both univariate and multivariate analysis were performed. Results The SA-group consisted of 451 patients and 34 patients were included in the SIM-group. 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. Conclusion 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 randomised study.

Introduction

One of the most prevalent perioperative complications of proximal femoral fracture surgery is delirium. An incidence up to 56% has been reported, although this varies, depending on the definition and diagnostic methods. It is associated with an increased mortality, prolonged admission time, discharge to a nursing home, impaired functional recovery and prognostic for cognitive impairments and dementia. Amongst the factors influencing the incidence of delirium during admissions are pain and systemic opioid use. Pain and systemic opioid use are both decreased by the administration of intrathecal morphine, which provides adequate analgesia for approximately 24 to 48 hours. 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. This claim seems questionable, since only one study investigated intrathecal morphine in proximal femoral fracture patients which detected no difference in complications, although it was underpowered for this outcome measure. Furthermore, studies involving intrathecal morphine in older patients undergoing elective hip surgery did not find an increased risk for postoperative delirium. 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 adds 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.

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. Data was used from all patients surgically treated using intrathecal anesthesia between 19-12-2016 and 14-01-2019. 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 was handled according to the Dutch Personal Data Protection Act. The methodology of the data collection and of any subsequent observational studies was approved by the institutional Medical Research Ethics Committee (METC Southwest Holland; protocol number 18-029) without the need of individual patient consent due to the observational nature of the study.

Data collection & patient selection

The patients’ characteristics and treatment outcomes were collected during admission, at the Emergency Department (ED), operation theatre and the medical ward by the treating physicians. Definitions of the complications, treatment aspects and data collection have been described previously in more detail by Sijp et al. 2017 for patients with a femoral neck fracture, but the data collection applies to all patients admitted with a proximal femoral fracture to the Haaglanden Medical Centre. Missing data was not imputed or replaced.
The patients were divided into two groups, based on the type of anesthesia that was administered (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.

Patient care

After radiological diagnosis of a proximal femoral fracture (AO-classification 3.1A/B and subtrochanteric fractures) on the ED, patients were prepared for admission to the surgical ward. Screening for cognitive impairments using the 6CIT was routinely performed in the ED for all older patients (age ≥70) without a known diagnosis of dementia or other cognitive impairments.13 The geriatric consultant was consulted for co-treatment during admission for all patients ≥70 years of age. An EKG and laboratory investigations (including full blood count, electrolytes and creatinine-levels) were performed and additional preoperative investigations were initiated when necessary.

Immediately after admission on the surgical ward the patients’ delirium risk was assessed using the (Dutch) National Safety Management System (VMS) theme ‘Frail Elderly’ by the ward nurses.14 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) scores.15 When delirium was suspected, a psychiatrist was consulted to diagnose delirium using the DSM-V criteria and for further treatment. Perioperative pain management is presented in Table 1. Regional nerve blocks were not routinely administered in this cohort.

Patients were ready for surgery when they were fastened, all pre-operative investigations and (if necessary) optimisation were performed and when the operating theatre was available. Surgical fracture treatment was performed according to the national guidelines and in accordance with the national surgical treatment protocol for proximal femoral fracture of the ‘Nederlandse Vereniging voor Heelkunde’ (Dutch Surgical Society).

All patients received a type of anesthesia depending on preference of the patient and the attending anesthesiologist. Only severe aortic valve stenosis (Aortic Valve Area < 0.8 cm2), pulmonary hypertension (mean Pulmonary Arterial Pressure > 50 mmHg) or coagulation disorders (PT>1.8 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. In a 10 ml syringe 1 ml of 10 mg/ml morphine was diluted with 9 ml NaCl 0.9%. After shaking the syringe, 9 ml was discarded and another 9 ml of NaCl 0.9% was drawn. Again, this mixture was shaken, and with a 3 ml syringe a dose of morphine was drawn and steriley injected in the syringe with bupivacaine for intrathecal injection. To administer the intrathecal injection, patients were sedated with propofol/esketamine or propofol/alfentanil for positioning, depending on the preference of the anesthesiologist. Commonly used dosages in our institution were 30-60 mg for propofol, 10-15 mg for esketamine, and 250 -500 mcg for alfentanil. 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 at a maximum of 2.5 mg/kg/hour.

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.

Patients returned to the surgical ward when they were hemodynamically stable, had an oxygen saturation > 94% with less than 4 L O2/min, reported a pain score < 4 on an NRS and had a Glasgow Coma Scale > 12 or had a mental state at least similar to the preoperative status. 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, 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. Twice weekly all patients were discussed in a multidisciplinary team meeting including a trauma- or orthopedic surgeon, ward doctor, geriatrician, ward nurse, physiotherapist, dietician and transfer nurse. The common goal was an uncomplicated recovery with discharge three days after surgery to an appropriate rehabilitation setting, depending on the patients premorbid living situation, functional recovery and comorbidities.

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

Outcomes

The primary outcome was defined as the occurrence of delirium during admission. 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.

Definitions
• Cognitive impairment was defined as previously diagnosed dementia or an abnormal 6-CIT score (≤11) used to screen for cognitive impairments during admission in the ED.\textsuperscript{13}
• Pain was scored three times daily during admission on a Numeric Rating Scale (NRS) with the range 0-10. Of each patient the highest postoperative pain score was registered.
• Systemic infections were pooled and included pneumonia, urinary tract infections and sepsis. It was scored when a patient had a core temperature ≥5 degrees of Celsius, elevated C Reactive Protein (CRP) levels (> 10 mg/L) or a White blood cell count > 12.5 * 10\(^9\)/ml, a clinically susceptible site of infection and (antibiotic) therapy was started. When the surgical site was involved, it was scored as a Post-Operative Wound Infection (POWI), either deep or superficial conform Dutch registration guidelines.\textsuperscript{16}
• 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.\textsuperscript{17}

\textit{Statistical analysis}

Patients were allocated according to their method of anesthesia, as described previously. Categorical variables were compared using the Chi-square test or, if the data was insufficiently large (expected cell counts ≤5) the Fisher’s exact test was used. Continuous data with a normal distribution are presented as median with the interquartile range (IQR) and compared using the independent sample T-test. Data with a non-normal distribution (Kolmogorov-Smirnov test of P< 0.05) are presented as median with the interquartile range (IQR) and compared using the Mann-Whitney U test. A multiple linear regression analysis was used to study the effect size of the anesthesia type (intrathecal anesthesia either with or without morphine) on the incidence of delirium during admission. The multivariate analysis adjusted for suspected confounding factors and factors identified with a P-value <0.1 in the univariate analysis. 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 Statistics version 25.0 (IBM, Amonk, New York).

\textit{Results}

A total of 1028 patients were admitted to the study hospital with a proximal femoral fracture between the 19\textsuperscript{th} of December 2016 and 14\textsuperscript{th} of January 2019. From these, 999 patients (97.1%) were treated surgically. 514 patients (50.7%) 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 and 150 µg. Baseline characteristics were comparable (Table 2). Of the treatment aspects only the operating time (skin-to-skin) differed significantly (SA: 52 minutes (10-164) vs. SIM: 69 minutes (27-129), P<0.001).

No statistically significant differences were observed in the clinical outcomes (Table 3). 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 affirms 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 4). In addition, other variables independently associated with delirium were a higher age (OR 1.050, 95%CI: 1.016-1.085; P=0.003), male sex (OR 0.455, 95%CI: 0.261-0.791; P=0.005), cognitive impairment (OR 1.950, 95%CI: 1.135-3.350; P=0.016) and fracture treatment with osteosynthesis (OR 0.476, 95%CI: 0.278-0.815; P=0.007).

\textit{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.

Pathogenesis of delirium is not fully elucidated, although multiple factors are associated with its occurrence.\textsuperscript{18} Well known risk factors are age, gender, ASA classification, premorbid cognitive impairment, fracture treatment, pain and medication use, one of which is opioids.\textsuperscript{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 accordance with other studies.\textsuperscript{21}

To date, only one study 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.\textsuperscript{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.
A possible mechanism by which intrathecal morphine reduces postoperative delirium is likely to involve reduced postoperative pain and reduced systemic opioid administration. Both factors are associated with delirium and reduced by the use of intrathecal morphine.\textsuperscript{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.\textsuperscript{22}

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.\textsuperscript{23} However, these analgesic methods may cause motor block which might hamper mobilisation 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.\textsuperscript{24-26} These disadvantages do not occur with intrathecal morphine, 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.

The use of intrathecal morphine is limited due to the association with delayed respiratory depression. However, the severity of respiratory depression has not been determined, which limits the interpretation of clinical relevance.\textsuperscript{27} Moreover, a dose of 300 mcg of intrathecal morphine has not been found to reduce ventilatory regulation in elderly patients\textsuperscript{28} and the optimal dose of intrathecal morphine for hip surgery is demonstrated to be 100 µg.\textsuperscript{9} Furthermore, a low dose of intrathecal morphine is believed to be safe, even in elderly patients, as long as no sedatives or additional systemic opioids are co-administered in the first 24 hours after surgery.\textsuperscript{5} Even though the current study found no cases of respiratory depression due to intrathecal morphine, the number of patients is too low to comment on the occurrence of delayed respiratory depression.

Age, male gender, pre-operative cognitive impairment and fracture treatment were the other independent variables associated with delirium found in this study. Age, gender and pre-operative cognitive impairments are known non-modifiable risk factors, demonstrated to be associated with delirium in multiple studies.\textsuperscript{19, 20} Treatment type of the fracture has not been associated directly with delirium previously.\textsuperscript{29} The observed association of delirium with treatment type of the fracture may be cement-mediated, since this may lead to pro-inflammatory molecules, negative hemodynamic effects and cerebral micro-embolisms.\textsuperscript{30, 31} However, the association between cement and delirium has not been confirmed previously in observational studies.\textsuperscript{29, 32}

Several important limitations inherent to our study design should be considered. Due to the observational nature of this study, no causative effect can be concluded. Furthermore, data originated from one centre. The vast majority of patients (93.0\%) was treated without intrathecal morphine due to an uneven division of the anesthesiologists based on their personal preference and professional experience. Other anesthesia- or anesthesiologist-related treatment aspects which may have differed between the minority group of anesthesiologists using intrathecal morphine and the other anesthesiologists, may have contributed to the observed study outcomes. Unfortunately, because 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 first mobilisation after surgery. Because these were unavailable, the hypothesized mechanism for the reduced incidence of delirium could not be tested in this study. Furthermore, the number of preoperative nerve blocks is low in both groups. These nerve blocks could decrease the use of preoperative opioids and pain scores, which might affect delirium as well.

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 postoperative period is the proposed mechanism that causes less delirium. This result urges for further exploration of this analgesic method on the occurrence of delirium in a randomised study, since this study carries a high risk of bias.

Declarations

Ethical statement: Ethical approval was obtained by the Medical Ethical Committee of Southwest Holland.

Publication consent: not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: No funding was obtained for this study.

Author's contribution:

MVK: initiated the study, interpreted the results and drafted the manuscript.

M v/d S: analysed the data, interpreted the results, was a major contributor to the manuscript.
RJS: interpreted the results, contributed to the manuscript.
AN: interpreted the results, contributed to the manuscript.

All authors have read and approved the final version of the manuscript.

Acknowledgements: We thank N. Heijmeskamp (Anesthesiologist, Haaglanden MC, The Hague, The Netherlands) for his contribution to the study.

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**Tables**

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