SDRP Journal of Anesthesia & Surgery

EPIDURAL ANALGESIA COMPARED WITH FEMORAL NERVE BLOCK FOR POSTOPERATIVE PAIN THERAPY AFTER TOTAL KNEE ARTHROPLASTY – A MATCHED PAIR ANALYSIS

Research ISSN:2473-2184

AUTHOR: Alf Kozian, M.D., Ph.D. May 2017

Johannes Jauch, M.D. [1]; Thomas Schilling, M.D., Ph.D., D.E.A.A. [2]; Dominik Brammen, M.D., D.E.S.A. [3]; Uwe Ebmeyer, M.D. [4]; Siegfried Kropf, Ph.D. [5]; Thomas Hachenberg, M.D., Ph.D. [6]; Alf Kozian, M.D., Ph.D. [7] (*), Kozian, M.D., Ph.D. [7]

1. *Consultant, Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg, Germany*
2. *Assistant Professor, Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg, Germany*
3. *Consultant, Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg, Germany*
4. *Professor, Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg, Germany*
5. *Professor, Institute for Biometrics and Medical Informatics, Otto-von-Guericke-University Magdeburg, Germany*
6. *Professor, Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg, Germany*
7. *Assistant Professor, Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg, Germany*

CONFLICTS OF INTEREST
There are no conflicts of interest for any of the authors.

Received Date: 22nd Apr 2017
Accepted Date: 15th May 2017
Published Date:19th May 2017

CORRESPONDENCE AUTHOR
Alf Kozian, M.D., Ph.D.
Dept. of Anesthesiology and Intensive Care Medicine
Otto-von-Guericke-University
Leipziger Str. 44
D-39120 Magdeburg
tel.: (+49) 0391-6713500
Fax: (+49) 0391-6714127
Email: Alf.Kozian@med.ovgu.de

ABSTRACT

Background:
Combined epidural analgesia (EA) and patient controlled analgesia (PCA) for postoperative pain control after total knee arthroplasty (TKA) is well established. Previous studies demonstrated the effectiveness of femoral nerve block (FNB) in combination with PCA. This study compares clinical efficiency and adverse events of pain therapy of an established (EA+PCA) and a modified (FNB+PCA) protocol.

Methods: A retrospective, single-center cohort study analyzing TKA patients after subarachnoid anesthesia. Matched pair analysis was performed using filters for American Society of Anesthesiologists (ASA) classification, age, gender, height, weight, comorbidities and prior use of analgesics. Surgical technique and postoperative medication protocol were similar in both groups. Primary outcome was postoperative pain on movement assessed by a visual analog scale (VAS) and use of analgesics within 72 hours after surgery. Secondary, incidence of adverse events (postoperative nausea and vomiting, pruritus, urinary retention and hypotension) was examined.

Results: From a total of 846 patients, 104 matched pairs were built and analyzed within 72 hours after surgery. Mean VAS scores were similar in patients receiving EA+PCA (2.7 ± 1.1) or FNB+PCA (2.8 ± 1.2). Supplemental opioid administration was higher in EA+PCA patients. Hypotension was more frequent in EA+PCA as in FNB+PCA patients (36 % vs. 12 %). Combined adverse events were more frequent in EA+PCA as in FNB+PCA patients (75 % vs. 58 %).

Conclusion: Both FNB+PCA and EA+PCA results in equivalent degrees of analgesia after TKA. Converting an established mode of pain therapy to a modified protocol may decrease incidence of adverse events rather than improve quality of analgesia.

Keywords: analgesia, epidural analgesia, femoral nerve block, postoperative pain, total knee arthroplasty

INTRODUCTION

The quality of postoperative pain therapy has a major impact on fast and functional recovery after total knee arthroplasty (TKA) [1]. Different modes of pain therapy have been applied including intravenously administered patient-controlled analgesia (PCA), wound infiltration with local anesthetics as well as epidural analgesia (EA) and femoral nerve blocks (FNB) [2]. Preferably, regional anesthesia after TKA would provide sufficient postoperative pain control, minimal additional analgesic requirements and enable faster recovery, and shorter hospital stay.

Most previous prospective studies have compared different modes of pain therapy in stringent protocols with high adherence to predefined schedules [3]. However, there are little data on efficacy and adverse effects of pain therapy after converting an established protocol (EA) to a modified protocol (FNB) [4, 5].

In the present retrospective matched pair analysis, the null hypothesis was tested that FNB would provide analgesia that is similar to EA as determined by pain scores, opioid use and incidence of severe side effects. The alternative hypothesis examined the relationship of occurrence of adverse events and the pain therapy approach.

MATERIALS & METHODS

The study was approved by the Ethics Committee of the Otto-von-Guericke University Magdeburg and was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, the guidelines for Good Clinical Practice (GCP) and the data protection act of the federal country Sachsen-Anhalt, Germany. The patients consent was waived for the reason of the retrospective study design.

A total of 846 patients was considered from the orthopedic department of Magdeburg University Hospital, Germany, from which 413 patients underwent total knee arthroplasty (TKA) with combined subarachnoid and epidural anesthesia, and 433 patients were scheduled for TKA under subarachnoid anesthesia and femoral nerve block.

Surgery: All patients received standard knee prosthesis via a medial para-patellar approach. The intervention was performed by an experienced team of four orthopedic surgeons in a standardized manner, both within groups and between groups.

A tight tourniquet was used to minimize blood loss and improve surgery conditions. No drains were left in the knee joint after surgery. A single intravenous dose of cefuroxime (1.5 g) was given for prophylactic antimicrobial chemotherapy and enoxaparine (20–40 mg) was administered subcutaneously for antithrombotic prophylaxis. Wound management includes ice packs and lower limb compression bandage according to routine procedures.

Regional anesthesia and postoperative pain management: In the EA group, subarachnoid anesthesia was performed as double needle technique [6]. A 25 G or 27 G Sprotte needle was placed in the lumbar subarachnoid space, and an epidural catheter was inserted approximately 4 cm cranially into the epidural space by means of an 18 G Tuohy needle. Hyperbaric bupivacaine (0.5 %, 2-3 ml) in combination with morphine (0.04 $mg \cdot ml^{-1}$) was injected for subarachnoid anesthesia. The first dose of the epidural local anesthetic (5-8 ml ropivacaine 0.2 %) was administered in the operating theatre at the end of surgery. The extent of the regional block was evaluated after admission to the recovery unit. Postoperatively, epidural catheter was used for pain control according to standard procedures on the peripheral ward.

In the FNB group, subarachnoid anesthesia was performed in a similar way. After identifying the lumbar subarachnoid space, 2-3 ml of hyperbaric bupivacaine 0.5 % plus 0.04 $mg \cdot ml^{-1}$ morphine was injected. Thereafter, a femoral nerve catheter was advanced using a neurostimulation technique to identify the correct needle position. The first dose of local anesthetic (15-20 ml ropivacaine 0.2 %) was administered via the femoral nerve catheter in the theatre. The quality of FNB was evaluated after transferring the patient to the recovery unit. Postoperatively, FNB was applied for pain control according to standard procedures on the peripheral ward.

After recovery from subarachnoid anesthesia, intravenous piritramide (0.05 -0.1 $mg \cdot kg^{-1}$) was titrated to

achieve sufficient pain relief. For pain assessment, a Visual Analog Scale (VAS, fig.1) with symbols and corresponding numbers reflecting the pain-level (0 = no pain; 1-3 = mild pain; moderate to severe pain = 4-6; very severe pain = 7-9; worst pain possible = 10) was used. Sufficient pain relief was defined as < 3 on this scale. After returning to the peripheral ward, all patients were treated with intravenous piritramide and non-opioid analgesics (metamizole, ibuprofen) according to standard protocols. In advance to physical therapy (30 min), 5-8 ml ropivacaine 0.2 % (EA) or 20 ml ropivacaine 0.2 % (FNB) were administered, respectively.

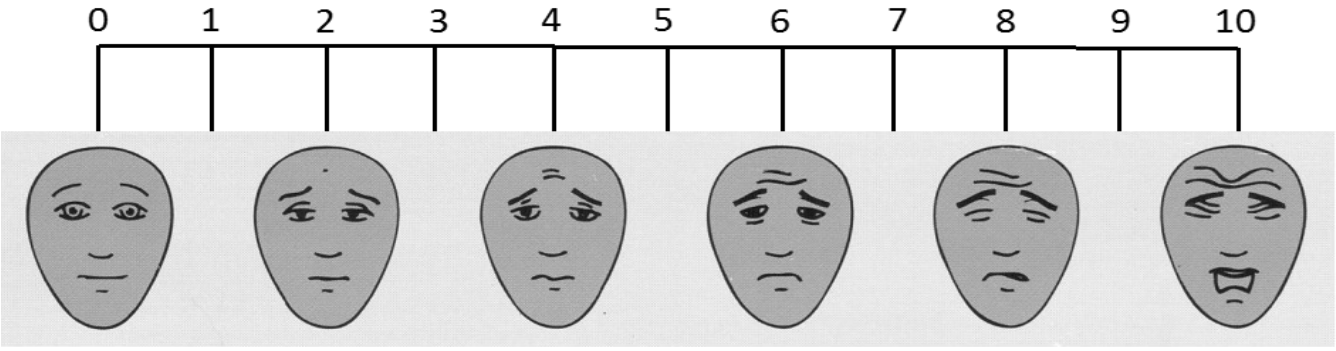

Figure 1: Scheme of a Visual Analog Scale (VAS) used in the study to evaluate the pain level

The patients were followed for the first three postoperative days in order to assess VAS and frequency of adverse events defined as postoperative nausea and vomiting (PONV), hypotension, itching, urinary retention, muscle weakness, neurological deficits and postoperative delirium. Adverse events were recorded at the routine daily ward round, at the discretion of hospital staff or if medication was necessary/administered (e.g. antiemetic drugs).

Outcome measures: The primary outcome measure was defined as postoperative VAS, both during physical therapy and at rest. Secondary outcome measures included opioid consumption for pain therapy, adverse events during pain therapy and length of hospital stay. The measurement intervals were defined as follows:

Day 0: day of surgery
Day 1: first postoperative day 0 – 24 hours
Day 2: second postoperative day 24 – 48 hours
Day 3: third postoperative day 48 – 72 hours

Statistical analysis: Statistical analysis was performed using computer software (SPSS, version 22; SPSS Inc., Chicago, IL). With reference to previous studies, power calculations on the basis of a two-sided design at a significance level of 5 % (= 0.05) and a probability of 80 % (β = 0.20) revealed that at least 44 patients were needed to detect a 50 % reduction in pain scores (VAS ± SD = 3 ± 2.5) [7], and to compare the analgesic efficiency and the occurrence of adverse events it would require at least 66 participants [8].
In order to consider the high inter-individual variability in primary and secondary outcomes, 208 patients were included.

All data were tested for normal distribution with the Shapiro-Wilks test. Non-normally distributed data were analyzed with the Mann-Whitney-U-Test, Pearson chi-square test and Fisher´s exact test, as appropriate. Results are presented as frequencies, mean (SD), or median with inter-quartile ranges (IQR). The level of significance was chosen to be 0.05.

RESULTS

A total of 846 patients underwent total knee arthroplasty in the orthopedic department of the University Hospital within a period of 2 years. A number of 506 patients scheduled for elective surgery (ASA physical status II-III, age > 18 years) were included in the study. The main exclusion criterion was conversion to general anesthesia.

The matching of the samples was performed using computer software EXCEL 2013 (Microsoft Corp, Redmond, WA). By using filters for ASA-classification, age, gender, height, weight, body mass index (± 2 kg·m

$^{-2}$), comorbidities and preoperative use of analgesics, 104 (matched) pairs were randomly generated. 298 patients were excluded from analysis because of comorbidities, preoperative analgesic use or missing data.

After matching for the predefined variables, 208 patients were included into the analysis. The patient characteristics are presented in table 1. Surgical outcome was favorable in all patients and length of hospital stay was similar in both groups.

	EA	FNB	p-value
Age (years), mean (±SD)	69 (±8.1)	70 (±7.9)	0.338
Height (cm), mean (±SD)	167.5 (±8.3)	165.0 (±8.5)	0.320
Weight (kg), mean (±SD)	83.4 (±16.6)	81.8 (±16.3)	0.332
BMI ($kg \cdot m^{-2}$), mean (±SD)	29.85 (±5.34)	29.52 (±5.54)	0.572
Gender (Male/female)	36/68	36/68	1.000
ASA 1/2/3	5/76/23	5/76/23	1.000
Preoperative analgesics n (%)	48 (46.2)	45 (43.3)	0.780
Diabetes mellitus, n (%)	19 (18.3.9)	21 (20.2)	0.861
Hypertension, n (%)	80 (76.9)	86 (82.7)	0.388
Duration of surgery (min), mean (±SD)	74 (±22)	68 (±27)	0.118

Table 1: Patient data

ASA American Society of Anesthesiologists, BMI body mass index, EA epidural analgesia, FNB femoral nerve block, There were no differences regarding VAS at movement between both patient groups up to 72 hours after TKA. The mean VAS scores were in patients receiving EA+PCA: 2.7 ± 1.1 vs. FNB+PCA: 2.8 ± 1.2.

During the postoperative course, more patients in the EA group needed additional intravenous opioids (piritramide) for pain relief as compared with the FNB group (fig. 2). Consumption of oral non-opioid analgesics was similar between both groups (fig. 3). The use of EA both for pain therapy at rest and prior to physical therapy was significantly lower on the second and third postoperative day as compared with FNB (fig. 4).

During the first 24 hours after TKA, 64 patients in the EA group and 66 patients in the FNB group suffered from nausea and vomiting (PONV). The incidence decreased to 31 patients, both in the EA group and in the FNB group, 24-48 hours after TKA. Within 48-72 hours after TKA, 7 patients (EA group) and 7 patients (FNB group) suffered from PONV without any significant differences between the groups.

In contrast, arterial hypotension was more frequent in the EA group in comparison with the FNB group (37 patients vs. 13 patients, $p < 0.001$). Likewise, combined adverse events (urinary retention, pruritus, muscle blockade) was 75 % in the EA group and 59 % in the FNB group, $p < 0.005$).

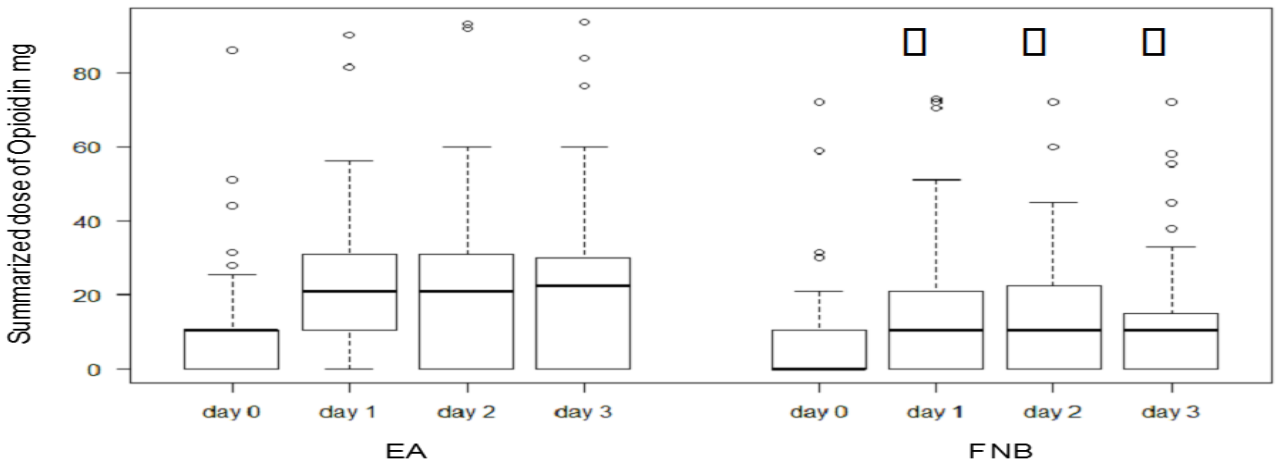

Figure 2: Summarized opioid (piritramide) consumption at day 0 (day of surgery) and in the postoperative course (day 1-3). Data are grouped for epidural analgesia (EA) or femoral nerve block (FNB) after total knee arthroplasty (TKA). Note that opioid consumption was lower when FNB was used for postoperative pain relief in comparison to EA (* $p<0.05$).

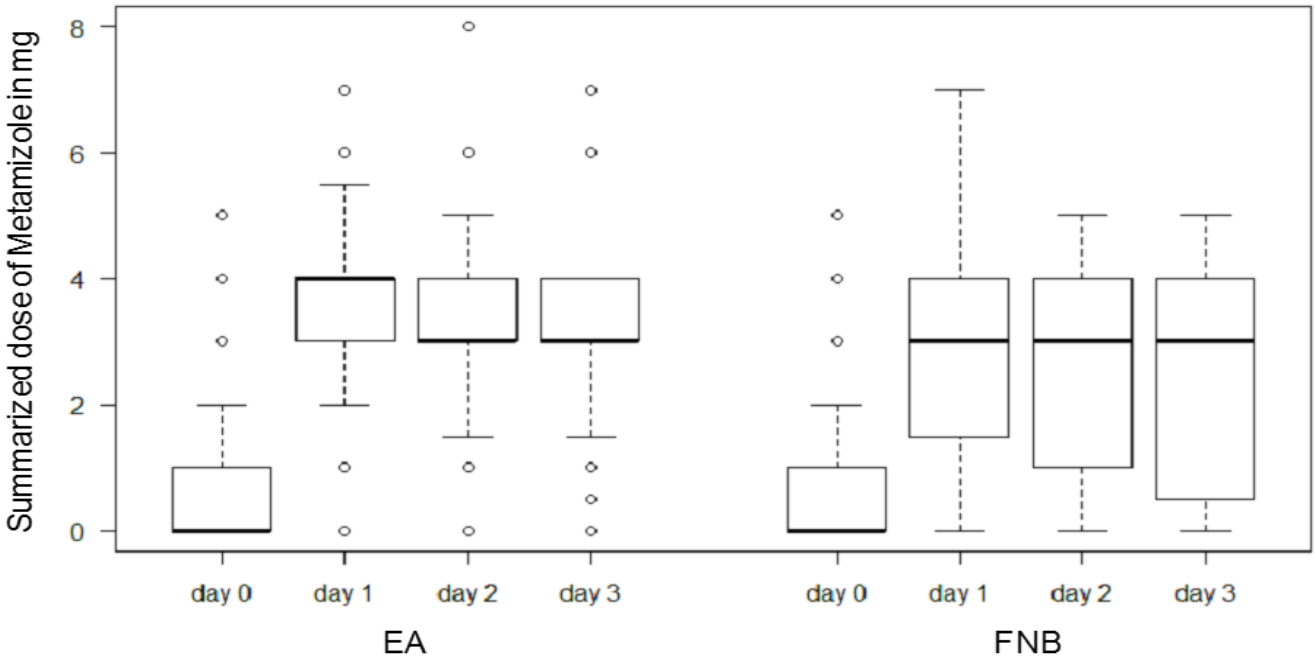

Figure 3: Summarized metamizole consumption at day 0 (day of surgery) and in the postoperative period (day 1-3). Data are grouped for epidural analgesia (EA) or femoral nerve block (FNB) after total knee arthroplasty (TKA). Note that equivalent metamizole doses were necessary for adequate pain therapy in both groups.

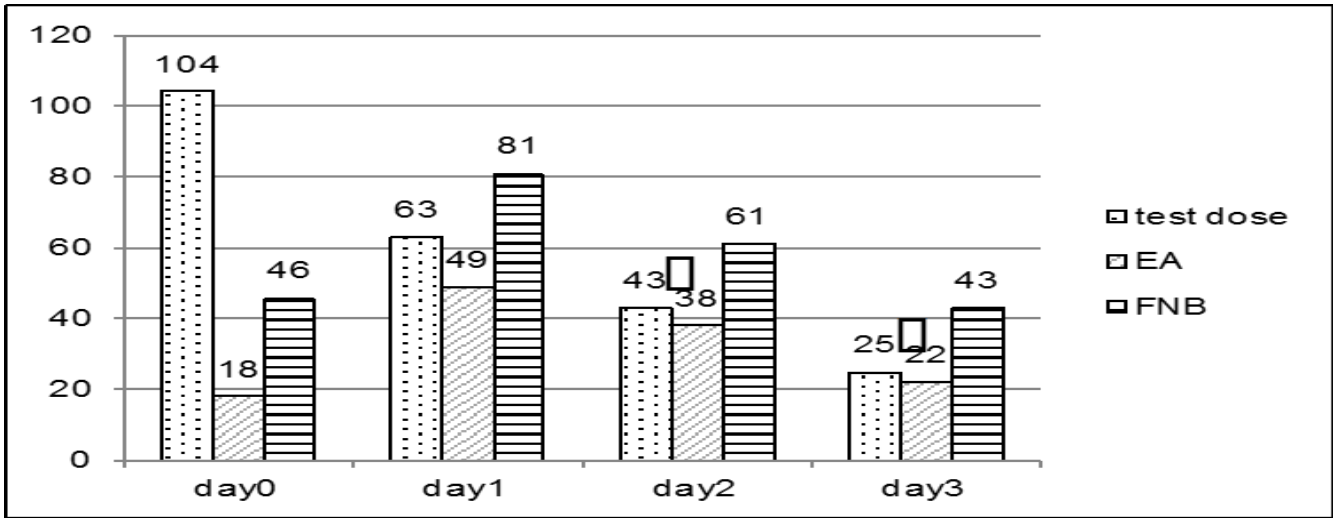

Figure 4: Frequency (numbers) of utilization of pain therapy at rest and prior to physical therapy at day 0 (day of surgery) and in the postoperative period (day 1-3). Data are displayed for test dose, epidural analgesia (EA) and femoral nerve block (FNB) after total knee arthroplasty (TKA). EA was used less fre-

DISCUSSION

The data of the present study demonstrate that the both regional anesthetic techniques, epidural analgesia and femoral nerve block, provide an adequate quality of postoperative pain therapy. Postoperative pain relief on movement in both groups was sufficient, indicated by a level of < 3 (mild pain) on the Visual Analog Scale.

Despite appropriate analgesia, supplemental consumption of intravenous opioids and metamizole on demand as well as combined adverse events were more frequent in patients who were scheduled for epidural analgesia.

The main indication for TKA is to improve function, pain relieve and to increase quality of life in patients with degenerative knee joint disease. TKA is a common surgical procedure with an age-standardized rate varying between 75 operations per 100000 in Norway, 132 operations per 100000 in Germany, 174 per 100000 in Switzerland and 221 per 100000 in the United States [9-14]. However, TKA in general is associated with significant postoperative pain [1]. Multimodal analgesic approaches including regional anesthesia techniques have been widely applied for postoperative pain therapy. Lumbar epidural analgesia in combination with patient controlled analgesia (PCA) has been considered to be the standard technique for pain control after hip surgery and knee replacement surgery [15].

However, placement of an epidural catheter carries a definite risk for neurological complications. Alternative techniques such as FNB combined with PCA or local anesthetic wound infiltration have been advocated for pain therapy after TKA [5].

Over two years all consecutive patients undergoing TKA under subarachnoid anesthesia were considered for a matched pair analysis. The American Society of Anesthesiologists (ASA) physical status classification system, age, gender and comorbidities were used for patient stratification. This approach is confirmed by a prospective study using the New Zealand Joint Registry. In 18434 patients undergoing orthopedic surgery, ASA class was associated with postoperative outcome, functional status and frequency of revision operations. The mean age, gender distribution, ASA classes and comorbidities in the present study are comparable to different studies on TKA [16, 17]. During both periods of time surgical techniques, regional anesthesia, postoperative care, and attending surgeons and anesthetists were unchanged. The matched pairs analysis was performed without using propensity scores to eliminate heterogeneity of the sample size. Thus our data reflect the analgesic management in a representative cohort of patients undergoing TKA.

Epidural anesthesia plus PCA has been used as a standard pain therapy after TKA for many years. The main reason to modify the perioperative pain therapy protocol was an increasing number of patients with defined contraindications against epidural catheterization. In addition, different studies have demonstrated that FNB may be an efficient mode of pain therapy after TKA although conflicting data had been published. The present data

demonstrate that, after converting postoperative pain therapy from EA plus PCA to FNB plus PCA, the quality of analgesia, physiotherapy, rehabilitation and surgical outcome have not been impaired. Moreover, piritramide consumption within 0 to 72 hours after TKA was significantly lower in the FNB group as compared to the EA group, which may significantly decrease the risk of postoperative respiratory depression. We did not observe less PONV despite a decreased opioid consumption during 0 to 48 hours postoperatively. This may be explained by a combination of bupivacaine and morphine for subarachnoid anesthesia. Although the quality of neuraxial blockade and duration of postoperative analgesia can be considerably improved by intrathecal morphine, the incidence of PONV may be even higher [18]. In addition, patients were treated with oral metamizole, which also may induce nausea and vomiting [19].

FNB plus PCA was associated with less episodes of arterial hypotension. The avoidance of hemodynamic complications has a major impact in surgical patients of higher age [20]. In particular, perioperative hypotensive episodes affect outcome after non-cardiac surgery [21]. Thoracic and lumbar epidural anesthesia induce sympathetic blockade and vasodilation in lower extremities. In patients with pre-existing hypertension, compensatory mechanisms are less efficient and may result in severe hypotension [22, 23].

FNB plus PCA is associated with less adverse events such as urinary retention, muscle blockade and pruritus. Although patient satisfaction after surgery is primarily affected by pain, adverse effects such as PONV and urinary retention have clearly an additional effect.

A pain therapy protocol using FNB plus PCA may exert advantages in orthopedic surgery of the lower extremities. Anti-coagulants are routinely used after major orthopedic surgery which may limit the applicability of epidural catheter techniques [24]. An unexpected finding was the rather lacking use of regional analgesia after TKA at rest and prior to physical therapy by the patients themselves. According to our standard procedures, orthopedic surgeons and staff nurses take care of pain management depending on the time schedule of physical therapy. A majority of patients received a test dose (3-5 ml ropicavaine 0.2 %) via the epidural catheter that was supplemented by intravenous and/or oral analgesics. Our data are in accordance with a previous study that demonstrated that staff nurses tend to accept higher VAS scores in patients with epidural catheters [25]. A prospective analysis describing a separate needle technique for combined subarachnoid and epidural analgesia revealed that 22 of 201 epidural catheters (almost 11 %) have not been used in the postoperative course [26]. Peripheral regional anesthesia may thus be favorable in orthopedic patients due to a higher acceptance by staff nurses and orthopedic surgeons.

Some remarks must be included to assess the limitations of the present study. First, patients undergoing TKA with general anesthesia were excluded. This may have influenced our results since postoperative pain therapy is different in patients with contraindications against neuraxial and/or peripheral blockade. Nevertheless, the vast majority of TKA was performed under subarachnoid anesthesia during both periods, and the bias from excluding patients with general anesthesia is likely small. In addition, intravenous piritramide was mostly used for postoperative pain therapy, which is common practice in Germany. Opioids with different pharmacokinetics and pharmacodynamics such as morphine may result in different analgesic levels after TKA [27, 28]. Finally, the results apply only to the immediate and short postoperative period of EA or FNB plus PCA in the PACU and on the peripheral ward. We were not able to follow our patients after discharging from the hospital. Thus, the prevalence and degree of chronic pain after TKA was not assessed.

CONCLUSIONS

Pain therapy using FNB plus PCA provides adequate analgesia in patients undergoing TKA. Converting an established mode of pain therapy to a modified protocol may decrease incidence of adverse events rather than improve the quality of analgesia.

AUTHOR´S CONTRIBUTIONS

Study design/planning: U.E., T.H., A.K. , Study conduct: J.J., U.E., A.K., Data analysis: J.J., D.B., T.S., S.K. Writing paper: J.J., T.H., A.K., T.S. , Revising paper: all authors

REFERENCE

1. Capdevila, X., et al., Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology, 1999. 91(1): p. 8-15.
2. Mistraletti, G., et al., Comparison of analgesic methods for total knee arthroplasty: metabolic effect of exogenous glucose. Reg Anesth Pain Med, 2006. 31(3): p. 260-9.
3. Sakai, N., et al., Continuous femoral versus epidural block for attainment of 120 degrees knee flexion after total knee arthroplasty: a randomized controlled trial. J Arthroplasty, 2013. 28(5): p. 807-14.
4. Nishio, S., et al., Comparison of Continuous Femoral Nerve Block, Caudal Epidural Block, and Intravenous

Patient-controlled Analgesia in Pain Control After Total Hip Arthroplasty: A Prospective Randomized Study. Orthop Rev (Pavia), 2014. 6(1): p. 5138.
5. Paul, J.E., et al., Femoral nerve block improves analgesia outcomes after total knee arthroplasty: a meta-analysis of randomized controlled trials. Anesthesiology, 2010. 113(5): p. 1144-62.
6. Puolakka, R., et al., Technical aspects and postoperative sequelae of spinal and epidural anesthesia: a prospective study of 3,230 orthopedic patients. Reg Anesth Pain Med, 2000. 25(5): p. 488-97.
7. Singelyn, F.J., et al., Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. Anesth Analg, 1998. 87(1): p. 88-92.
8. Barrington, M.J., et al., Continuous femoral nerve blockade or epidural analgesia after total knee replacement: a prospective randomized controlled trial. Anesth Analg, 2005. 101(6): p. 1824-9.
9. Cots, F., et al., Patient classification systems and hospital costs of care for knee replacement in 10 European countries. Health Econ, 2012. 21 Suppl 2: p. 116-28.
10. Kurtz, S.M., et al., Impact of the economic downturn on total joint replacement demand in the United States: updated projections to 2021. J Bone Joint Surg Am, 2014. 96(8): p. 624-30.
11. Pabinger, C. and A. Geissler, Utilization rates of hip arthroplasty in OECD countries. Osteoarthritis Cartilage, 2014. 22(6): p. 734-41.
12. Pabinger, C., H. Lothaller, and A. Geissler, Utilization rates of knee-arthroplasty in OECD countries. Osteoarthritis Cartilage, 2015. 23(10): p. 1664-73.
13. Robertsson, O., et al., Knee arthroplasty in Denmark, Norway and Sweden. A pilot study from the Nordic Arthroplasty Register Association. Acta Orthop, 2010. 81(1): p. 82-9.
14. Schafer, T., et al., Trends and geographical variation of primary hip and knee joint replacement in Germany. Osteoarthritis Cartilage, 2013. 21(2): p. 279-88.
15. Choi, P.T., et al., Epidural analgesia for pain relief following hip or knee replacement. Cochrane Database Syst Rev, 2003(3): p. CD003071.
16. Hunt, L.P., et al., 45-day mortality after 467,779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: an observational study. Lancet, 2014. 384(9952): p. 1429-36.
17. Liddle, A.D., et al., Adverse outcomes after total and unicompartmental knee replacement in 101,330 matched patients: a study of data from the National Joint Registry for England and Wales. Lancet, 2014. 384(9952): p. 1437-45.
18. Murphy, P.M., et al., Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. Anesth Analg, 2003. 97(6): p. 1709-15.
19. Jage, J., et al., [Postoperative pain therapy with piritramide and metamizole. A randomized study in 120 patients with intravenous on-demand analgesia after abdominal surgery.]. Schmerz, 1990. 4(1): p. 29-36.
20. Plante, A., E. Ro, and J.R. Rowbottom, Hemodynamic and related challenges: monitoring and regulation in the postoperative period. Anesthesiol Clin, 2012. 30(3): p. 527-54.
21. Walsh, M., et al., Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology, 2013. 119(3): p. 507-15.
22. Davies, P. and H. Howells, Hypotension following combined spinal epidural anaesthesia. Anaesthesia, 2003. 58(9): p. 932.
23. Hopf, H.B., R. Schlaghecke, and J. Peters, Sympathetic neural blockade by thoracic epidural anesthesia suppresses renin release in response to arterial hypotension. Anesthesiology, 1994. 80(5): p. 992-9.
24. Quinlan, D.J. and B.I. Eriksson, Novel oral anticoagulants for thromboprophylaxis after orthopaedic surgery. Best Pract Res Clin Haematol, 2013. 26(2): p. 171-82.
25. Davies, A.F., et al., Epidural infusion or combined femoral and sciatic nerve blocks as perioperative analgesia for knee arthroplasty. Br J Anaesth, 2004. 93(3): p. 368-74.
26. Cook, T.M., 201 combined spinal-epidurals for anaesthesia using a separate needle technique. Eur J Anaesthesiol, 2004. 21(9): p. 679-83.
27. Abou Hammoud, H., et al., Intravenous morphine titration in immediate postoperative pain management: population kinetic-pharmacodynamic and logistic regression analysis. Pain, 2009. 144(1-2): p. 139-46.
28. Bouillon, T., et al., Population pharmacokinetics of piritramide in surgical patients. Anesthesiology, 1999. 90(1): p. 7-15.

SIFT DESK
E-mail: helpdesk@siftdesk.org , visit us on the web at: **www.siftdesk.org**