Review article

Chronified Pain Following Operative Procedures

The Place of Locoregional and Systemic Local Anesthetics

Dominik Geil, Claudia Thomas, Annette Zimmer, and Winfried Meissner

Summary

Background: Over 18 million operative procedures are performed each year in Germany alone. Approximately 10% of surgical patients develop moderate to severe chronic post-surgical pain (CPSP), which can severely impair their quality of life. The pain must persist for at least three months to be called chronic; pain that arises after a symptom-free interval is not excluded. The perioperative use of local anesthetic agents may lessen the incidence of CPSP.

Methods: We selectively reviewed the pertinent literature, including two current Cochrane Reviews. Local and regional anesthetic techniques are discussed, as is the intravenous administration of lidocaine.

Results: The main risk factors for CPSP are pre-existing (preoperative) chronic pain, opioid intake, a pain-related catastrophizing tendency, intraoperative nerve injury, and severe acute postoperative pain. CPSP is reported to be especially common after thoracic surgery, breast surgery, amputations, and orthopedic procedures. Local and regional anesthetic techniques have been shown to significantly lower the incidence of CPSP after thoracotomy (number needed to treat for an additional beneficial outcome [NNTB] = 7), breast cancer surgery (NNTB = 7), and cesarean section (NNTB = 19). Intravenous lidocaine also lowers the incidence of CPSP after various types of procedures.

Conclusion: Local and regional anesthetic techniques and intravenous lidocaine lower the incidence of CPSP after certain types of operative procedures. The intravenous administration of lidocaine to prevent CPSP is off label and requires the patient's informed consent. The evidence for the measures presented here is of low to medium quality.

Cite this as:
Geil D, Thomas C, Zimmer A, Meissner W: Chronified pain following operative procedures—the place of locoregional and systemic local anesthetics. Dtsch Arztebl Int 2019; 116: 261–6. DOI: 10.3238/arztebl.2019.0261

Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital: Dr. med. Dominik Geil, Dr. med. Claudia Thomas, Dr. med. Annette Zimmer, Apl. Prof. Dr. med. Winfried Meißner

Postoperative pain resolves rapidly in most patients who undergo surgery, but some complain weeks or months afterward of persistent pain in the area of the procedure. Since the first description of chronic post-surgical pain (CPSP) (1), many publications have appeared on its incidence, risk factors, and potential preventive measures. The reported incidence and severity of CPSP after various types of procedure varies markedly depending on the relevant definitions and designations, making comparisons across studies difficult. It is nonetheless clear, in view of the large and growing number of surgical procedures that are now performed—more than 18 million per year in Germany alone (2), and more than 312 million per year worldwide (3)—that this phenomenon is a matter of the first importance not only in clinical medicine, but also in health policy and economics (4).

We use the designation "chronic post-surgical pain" (CPSP) rather than the alternative, "persistent postoperative pain" [PPP], because it has been found that chronification does not always consist of the prolongation and persistence of the acute pain that was present after surgery. Rather, in some cases, CPSP arises after a pain-free interval (5). The modified criteria of Werner and Kongsgaard (6) *(Box)* serve as a basis for the inclusion of CPSP in the new edition of the International Classification of Diseases, the ICD-11 (7). These criteria, however, were not uniformly applied in the sources we evaluated in preparing the current review.

In this article, we describe the frequency and mechanisms of CPSP and the potential utility of local and regional anesthetic techniques to prevent the post-surgical chronification of pain.

Method

We qualitatively searched the literature for relevant publications on the frequency, risk factors, and mechanisms of chronic postoperative pain. To determine the preventive effect, if any, of regional anesthetic techniques, we made use of two current Cochrane Reviews (8, 9), which included publications up to the years 2015 and 2016, respectively. For more recent literature, we selective searched medical databases using a search strategy similar to those of the Cochrane Reviews, in order to cover the period up to

BOX

Definition*

Chronic post-surgical pain is defined as pain that meets the following criteria:

- Pain develops after a surgical procedure or increases in intensity after the surgical procedure.
- Pain should be of at least 3 months' duration with a significant negative effect on the quality of life
- Pain is either a continuation of acute post-surgery pain or may develop after an asymptomatic period
- Pain is either localized to the surgical field or to a referred area (e.g. innervation territory, referred dermatome for visceral surgery)
- Other possible causes for the pain have been excluded (e.g. infection, cancer recurrence)

* modified from Werner and Kongsgaard (6)

mid-2018. One Cochrane review (9) included studies on intravenous lidocaine administration. We therefore decided to discuss this technique as well in our review, even though it is a systemic rather than local or regional anesthetic technique.

Frequency

The reported frequencies of CPSP vary widely depending on the patient collective studied, the type of operation performed, the time elapsed since surgery, the definition of CPSP, and the method of analysis (5, 10, 11). In a survey (part of the PAIN OUT project) of 1 044 patients who had undergone various types of surgery, 13.1% said they had persistent pain of intensity 3–5 on the Numerical Rating Scale (NRS) in the area of the procedure six months later, and 2.9% reported pain of intensity 6 or more (0 = no pain, 10 = the most intense pain imaginable). By one year after surgery, these figures declined to 9.6% and 2.2%, respectively (12).

CPSP is reportedly especially common after thoracic surgery, breast surgery, amputations, and orthopedic procedures (11, 12). 15–50% of patients with CPSP report that their pain has a neuropathic component (11). Neuropathic manifestations are associated with higher pain intensity, marked functional impairment, and poorer quality of life (12).

The incidence of CPSP after outpatient surgical procedures has been estimated at 15.3% (13). In children, the reported incidence of CPSP is 11% (14). In principle, CPSP can arise after any kind of surgical procedure.

Risk factors

Preoperative risk factors

Preoperatively existing chronic pain, either in the region to be operated on or elsewhere, is a risk factor for the development of CPSP (15, 16). Preoperative opioid use in women about to undergo gynecological surgery is associated with a markedly higher postoperative incidence of CPSP (17). Psychological risk factors are currently controversial, but it seems that a catastrophizing tendency, thought focusing, a feeling of being under excessive stress, and an anxious tendency are linked to a higher risk of CPSP, particularly when these features are associated with pain (18). In contrast to these clinical factors, it has not yet been possible to identify any genetic, histological, or biochemical biomarker that is associated with the development of CPSP (19). An association of altered cutaneous sensitivity, as revealed by a preoperative Quantitative Sensory Test (QST), with CPSP has been observed in only a few cases and seems to be of little predictive value (20).

Intraoperative risk factors

Certain specific types of operation seem to elevate the risk of CPSP, and the nature, extent, and invasiveness of operative trauma may elevate it as well (e.g., axillary dissection in breast cancer surgery, video-assisted thoracoscopy vs. open thoracotomy [21]). Intraoperative nerve injury is considered an important pathophysiological risk factor of chronification mechanisms (22).

Postoperative risk factors

Nearly all studies have revealed a very close association between (acute) postoperative pain on the one hand and CPSP on the other. Aside from the absolute intensity of the pain, the duration of severe pain (e.g., the first 24 hours after surgery) is a risk factor (16). It is unclear, however, whether the relation between intense acute pain and chronic pain is one of cause and effect, for both may be epiphenomena that reflect a common pathogenetic mechanism. Postoperative neuropathic pain is likewise a risk factor for CPSP (23). Moreover, similar psychological factors seem to be at work before and after surgery. The role played by post-surgical complications (e.g., wound infection) is controversial. Twelve months after discharge from the intensive care unit, 16% of patients report chronic pain of intensity 4 or more (NRS) that was not present before admission (24).

Mechanisms

Unlike the mechanisms underlying acute postoperative pain (25), those underlying CPSP have received little scientific attention to date.

For detailed discussions, we refer the reader to the publications of Richebé et al. (26) and Chapman et al. (27). The latter postulates five mechanisms that can contribute to the development of CPSP, either alone or in combination:

- peripheral sensitization via inflammation and/or nerve injury.
- maladaptive central neural plasticity at spinal and higher levels (central sensitization), caused by opioids (particularly when given preoperatively), stress, and other factors.

TABLE

Findings of the Cochrane analysis concerning CPSP after non-orthopedic surgery*1

Surgical procedure	Regional anesthetic technique	Studies (n)	Prevention of CPSP OR [95% CI]
Thoracotomy*2	Epidural anesthesia, wound infiltration, intercostal block	7	0.52 [0.32; 0.84]
Breast cancer surgery*3	Paravertebral block	6	0.61 [0.39; 0.97]
	Intravenous lidocaine*2	2	0.24 [0.08; 0.69]
	Local infiltration	6	0.29 [0.12; 0.73]
Cesarean section*2	RA (various techniques)*4	4	0.46 [0.28; 0.78]
Iliac crest bone harvesting*2	Local anesthesia	3	0.20 [0.04; 1.09]

*1 Weinstein et al. (9), *2 medium-quality evidence, *3 low-quality evidence, *4 in addition to spinal anesthesia
CPSP, chronic post-surgical pain; CI, confidence interval; n, number of included studies; OR, odds ratio; RA, regional analgesia

- compromised descending nociceptive inhibition: among other factors, it has been hypothesized that the excessive administration of exogenous opioids can impair the functioning of this system via negative feedback.
- pathological descending nociceptive facilitation: among other factors, cognitive factors such as expectations, anxiety, and a catastrophizing tendency can apparently influence the systems that inhibit and facilitate pain, yielding both placebo and nocebo effects.
- alterations of brain function, connectivity, and structure (cerebral plasticity), for example, in phantom pain. Changes in the representative zones of the sensory cortex can be associated with the generation and disappearance of phantom pain and other types of pain.

In general, however, these proposed mechanisms have not been studied with reference to a CPSP model, and not at all in human beings. They also only partly integrate the potential role of some of the risk factors listed above, e.g., psychosocial variables. They do, however, provide a useful framework of hypotheses that can motivate future research in the field.

Prevention of CPSP with local and regional anesthetic techniques

An overview of the relevant study findings with respect to surgery other than orthopedic surgery is given in the *Table*.

Thoracotomy

A meta-analysis of randomized, controlled trials, by Weinstein et al. (9), revealed a reduction of the risk of CPSP after thoracotomy by the intraoperative use of regional anesthesia in addition to general anesthesia *(Table)*. Seven patients need to be so treated to prevent one case of CPSP, i.e., the number needed to treat for an additional beneficial outcome (NNTB) is 7. A larger benefit was found when only the five studies of epidural anesthesia were considered (NNTB = 5).

Breast cancer surgery

A Cochrane analysis of 18 studies, which included a total of 1297 patients, revealed a reduction of the risk of chronic pain after breast cancer surgery through the intraoperative use of regional analgesia (RA) in addition to general anesthesia (NNTB = 7) *(Figure)*. A larger benefit was found when only the studies of intravenous lidocaine were considered (NNTB = 4) (9).

Two further publications on the use of intravenous lidocaine (28, 29) and four randomized, controlled trials (RCTs) on the use of paravertebral blockade after breast cancer surgery also indicate a preventive effect on CPSP. Multilevel paravertebral blockade seems to be particularly effective (30).

Cesarean section

Four RCTs on CPSP after cesarean section, including a total of 551 patients, were studied in the meta-analysis by Weinstein et al. (9). It was concluded that the use of RA in addition to spinal anesthesia lowers the risk of CPSP (NNTB = 19) (9). A tranversus abdominis plane block was used in two of these trials, while infiltration of the wound edges and peritoneal instillation of a local anesthetic were used in one trial each.

Iliac crest bone harvesting

Weinstein et al. also reported evidence of a preventive effect of intraoperative local anesthesia on CPSP after iliac crest bone harvesting, but the individual studies included in the analysis employed different endpoints and were thus hard to compare with each other (9).

Further surgical procedures

Studies have shown that the use of regional anesthetic in prostatectomy, hysterectomy, or amputations has no effect on CPSP. There is as yet inadequate evidence to judge the possible effect of RA after cardiac surgery, laparotomy, herniotomy, spinal surgery, and thyroidectomy (9). Two RCTs (31, 32) showed a preventive effect of intravenous lidocaine and of wound-edge infiltration (respectively) after nephrectomy, but the

Figure: Wound-edge infiltration with ropivacaine after surgery on the right breast for cancer. In addition to the incision, the drain exit site is infiltrated as well. (Reproduced with the kind permission of R. Riese, Clinical Media Center, Jena University Hospital, Jena, Germany.)

postoperative follow-up interval in one of these trials was only one month (31).

Knee replacement surgery

In a Cochrane review concerning joint surgery, in which only RCTs were included in the analysis, the outcome parameters in the various trials were so different that data from only three trials could be pooled. The range of knee movement was the primary endpoint, serving as a surrogate parameter for joint function (8). Regional analgesia was not found to have any statistically significant effect on the frequency of CPSP three months after surgery.

A randomized, controlled trial published in 2015 showed the superiority of a continuous femoral nerve block over patient-controlled analgesia (PCA) with intravenous opioids, not only with respect to the incidence of CPSP, but also with respect to joint function three and six months after knee replacement (33). Comparisons of different RA techniques in randomized, controlled trials did not reveal any differences with respect to the incidence of CPSP:

- femoral nerve vs. adductor block (34)
- epidural anesthesia vs. local infiltrational anesthesia (LIA) (35)
- single-shot vs. continuous LIA (36)
- LIA vs. systemic analgesia (37).

Hip surgery

Three trials on the use of RA to prevent CPSP after hip surgery (LIA vs. systemic analgesia [37], single-shot LIA vs. repeated local anesthetic (LA) boli [38], and LIA vs. systemic analgesia [39]) yielded inconsistent results.

Discussion

The best evidence concerning the prevention of CPSP is for the perioperative use of epidural analgesia in thoracotomy, and of paravertebral blockade or intravenous lidocaine administration in breast cancer surgery. In each of these situations, four to seven patients must be treated for a single clinically relevant case of CPSP to be prevented. In view of these findings, we suggest that these preventive measures should always be applied unless there is a valid reason for not applying them; all the more so because they also markedly lessen the pain intensity and analgesic requirement in the early postoperative phase (40).

The use of regional or local analgesia in addition to spinal anesthesia has been shown to lower the incidence of CPSP after caesarean section. Marked chronic post-surgical pain is rarer after cesarean section than after chest surgery or breast cancer surgery (e1) (and the NNTB is correspondingly higher), but cesarean section is one of the most common operations (232 505 of them were performed in Germany in a single year [e2]). The available studies have not shown any particular RA technique to be superior to the others for this purpose.

In the Cochrane analysis concerning iliac crest graft harvesting (9), the inclusion criteria of the individual studies under analysis (with dichotomization of the CPSP endpoint) led to the exclusion of one out of four studies. As a result, no significant preventive effect of local analgesia was demonstrable. The use of this technique should nonetheless be considered, as it can be performed easily and with practically no risk.

The interpretation of the protective effect of RA in nephrectomy, as revealed by two studies, is hampered by the fact that one of these studies, though otherwise methodologically sound, included only one month of postoperative follow-up (31). The evidence is, therefore, limited, and nephrectomy is not a very common procedure. It is, however, one of the most acutely painful urological operations (e3), and this alone would seem to justify the use of RA.

Which methods of analgesia have been found to be especially effective? In the thoracotomy studies, regional analgesic techniques were most commonly used. In breast cancer surgery, paravertebral blockade, local infiltration, and intravenous lidocaine administration were used; the odds ratios for the benefit of the latter two techniques were more favorable than that of paravertebral blockade *(Table)*. If one also considers the ease of application and the potential complications, then wound-edge infiltration and systemic lidocaine are the main techniques to be recommended for CPSP prophylaxis in breast cancer surgery.

There have been many studies on the use of intravenous lidocaine to prevent CPSP after various surgical procedures. Two relevant meta-analyses have been published, one on breast cancer surgery (three underlying studies [e4]) and one on a mix of surgical procedures (six underlying studies [e5]). The authors of both analyses conclude that intravenous lidocaine can lower the incidence of CPSP. The mechanism of action of systemic lidocaine is not fully understood.

The benefit of local and regional analgesic techniques may, in fact, be partly due to the systemic effects of the local anesthetic drugs used: whenever regional analgesia is performed, some of the local anesthetic is resorbed into the systemic circulation.

It is thus recommended for clinical practice that intravenous lidocaine should always be given when an indicated, or planned regional analgesia cannot be performed—particularly in view of the fact that intravenous lidocaine is also recommended for the treatment of acute pain (40). In the authors' institution, a lidocaine bolus of 1.5 mg/kg body weight is given as a rapid infusion, followed by a continuous infusion of 1.5 mg/kg×hr until ca. 30 minutes before the patient's transfer out of a monitored area (recovery room, intensive care unit, or intermediate care unit) (e6).

As this use of lidocaine is off label, the patient must be informed specifically, and in advance, of its benefits, risks, and side effects, and must give informed consent. As long as the dosages mentioned above are adhered to, complications such as cardiac arrhythmia or epileptic seizures are extremely rare.

Conclusion

Chronic pain after operative procedures is a clinically relevant problem whose frequency should not be underestimated. Tissue damage, inflammation, nerve injury, and pre-existing and postoperative pain, in addition to psychological factors, can alter the nociceptive signaling pathways on multiple levels. As a result, pain can persist for months or years after an operation, or can re-emerge after a pain-free interval. After some types of surgery, local or regional analgesic techniques seem to be able to lessen such chronification processes or prevent them entirely. This is particularly true of epidural anesthesia in thoracotomy and of local infiltration with LA or systemic lidocaine administration in breast cancer surgery.

It would be desirable for future interventional trials in pain therapy to contain not just documentation of the patients' acute postoperative pain, but also long-term observation for the better assessment of the effects of RA and LA on chronic post-surgical pain.

Conflict of interest statement
Prof. Meissner has received lecture honoraria from the BioQ Pharma, TAD Pharma, Mundipharma International Limited, Grünenthal, and Menarini companies and has served as a paid advisor to Grünenthal and Sanofi. He has also received third-party research support from the European Society of Anaesthesiology (ESA).
Dr. Geil has received reimbursement of scientific meeting participation fees and travel expenses from the German Society for Anesthesiology and Intensive Care Medicine *(Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin).*

The other authors state that they have no conflict of interest.

Manuscript submitted on 20 November 2018, revised version accepted on 18 February 2019.

Translated from the original German by Ethan Taub, M.D.

Key messages

- Chronic post-surgical pain (CPSP) is an important clinical problem because of the large number of surgical procedures performed in Germany and worldwide every year.
- Six months after surgery, the frequency of CPSP with a pain intensity of 3-5, or of ≥ 6, on the ten-point NRS scale is approximately 13% and 3%, respectively.
- Preoperative pain and opioid use, a catastrophizing tendency, and acute pain after a surgical procedure—e.g., in the first 24 hours—promote the development of CPSP.
- The preoperative assessment of risk factors for CPSP can help identify patients at high risk, who can then be treated prophylactically with regional analgesia or intravenous lidocaine administration.
- Alongside the use of local and regional anesthetic techniques, there is also evidence that systemic lidocaine administration can lower the incidence of CPSP.

References

1. Crombie IK, Davies HT, Macrae WA: Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain 1998; 76: 167–71.
2. Gesundheitsberichterstattung des Bundes: Operationen der vollstationären und ambulanten Patientinnen und Patienten. Daten von 2017: www.gbe-bund.de/gbe10/I?I=662:36191304D und www.gbe-bund.de/gbe10/I?I=606:36191324D. (last accessed on 12 March 2019).
3. Weiser TG, Haynes AB, Molina G, et al.: Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet 2015; 385 (Suppl 2): S11.
4. Guertin PM, Tarride JE, Talbot D, Watt-Watson J, Choinière M: Just how much does it cost? A cost study of chronic pain following cardiac surgery. J Pain Res 2018; 11: 2741–59.
5. Lavand'homme P: 'Why me?' The problem of chronic pain after surgery. Br J Pain 2017; 11: 162–5.
6. Werner MU, Kongsgaard UE: I. Defining persistent post-surgical pain: is an update required? Br J Anaesth 2014; 113: 1–4.
7. Treede RD, Rief W, Barke A, et al.: A classification of chronic pain for ICD-11. Pain 2015; 156: 1003–7.
8. Atchabahian A, Schwartz G, Hall CB, Lajam CM, Andreae MH: Regional analgesia for improvement of long-term functional outcome after elective large joint replacement. Cochrane Database Syst Rev 2015: Cd010278.
9. Weinstein EJ, Levene JL, Cohen MS, et al.: Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. Cochrane Database Syst Rev 2018; 6: Cd007105.
10. Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A: Persistent postsurgical pain in a general population: prevalence and predictors in the Tromso study. Pain 2012; 153: 1390–6.
11. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS: The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain 2013; 154: 95–102.
12. Fletcher D, Stamer UM, Pogatzki-Zahn E, et al.: Chronic postsurgical pain in Europe: an observational study. Eur J Anaesthesiol 2015; 32: 725–34.
13. Hoofwijk DM, Fiddelers AA, Peters ML, et al.: Prevalence and predictive factors of chronic postsurgical pain and poor global recovery one year after outpatient surgery. Clin J Pain 2015; 31: 1017–25.
14. Batoz H, Semjen F, Bordes-Demolis M, Benard A, Nouette-Gaulain K: Chronic postsurgical pain in children: prevalence and risk factors. A prospective observational study. Br J Anaesth 2016; 117: 489–96.
15. Althaus A, Hinrichs-Rocker A, Chapman R, et al.: Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain 2012; 16: 901–10.
16. Fletcher D, Stamer UM, Pogatzki-Zahn E, et al.: Chronic postsurgical pain in Europe: an observational study. Eur J Anaesthesiol 2015; 32: 725–34.

17. van den Kerkhof EG, Hopman WM, Goldstein DH, et al.: Impact of perioperative pain intensity, pain qualities, and opioid use on chronic pain after surgery: a prospective cohort study. Reg Anesth Pain Medicine 2012; 37: 19–27.
18. Caumo W, Schmidt AP, Schneider CN, et al.: Preoperative predictors of moderate to intense acute postoperative pain in patients undergoing abdominal surgery. Acta Anaesthesiol Scand 2002; 46: 1265–71.
19. Montes A, Roca G, Sabate S, et al.: Genetic and clinical factors associated with chronic postsurgical pain after hernia repair, hysterectomy, and thoracotomy: a two-year multicenter cohort study. Anesthesiology 2015; 122: 1123–41.
20. Martinez V, Uceyler N, Ben Ammar S, et al.: Clinical, histological, and biochemical predictors of postsurgical neuropathic pain. Pain 2015; 156: 2390–8.
21. Bendixen M, Jorgensen OD, Kronborg C, Andersen C, Licht PB: Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. Lancet Oncol 2016; 17: 836–44.
22. Alfieri S, Rotondi F, Di Giorgio A, et al.: Influence of preservation versus division of ilioinguinal, iliohypogastric, and genital nerves during open mesh herniorrhaphy: prospective multicentric study of chronic pain. Ann Surg 2006; 243: 553–8.
23. Beloeil H, Sion B, Rousseau C, et al.: Early postoperative neuropathic pain assessed by the DN4 score predicts an increased risk of persistent postsurgical neuropathic pain. Eur J Anaesthesiol 2017; 34: 652–7.
24. Baumbach P, Gotz T, Gunther A, Weiss T, Meissner W: Prevalence and characteristics of chronic intensive care-related pain: the role of severe sepsis and septic shock. Crit Care Med 2016; 44: 1129–37.
25. Pogatzki-Zahn EM, Segelcke D, Schug SA: Postoperative pain-from mechanisms to treatment. Pain Rep 2017; 2: e588.
26. Richebe P, Capdevila X, Rivat C: Persistent postsurgical pain: pathophysiology and preventative pharmacologic considerations. Anesthesiology 2018; 129: 590–607.
27. Chapman CR, Vierck CJ: The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. J Pain 2017; 18: 359 e1–38.
28. Kim MH, Lee KY, Park S, Kim SI, Park HS, Yoo YC: Effects of systemic lidocaine versus magnesium administration on postoperative functional recovery and chronic pain in patients undergoing breast cancer surgery: a prospective, randomized, double-blind, comparative clinical trial. PLoS One 2017; 12: e0173026.
29. Kendall MC, McCarthy RJ, Panaro S, et al.: The effect of intraoperative systemic lidocaine on postoperative persistent pain using initiative on methods, measurement, and pain assessment in clinical trials criteria assessment following breast cancer surgery: a randomized, double-blind, placebo-controlled trial. Pain Pract 2018; 18: 350–9.
30. Hussain N, Shastri U, McCartney CJL, et al.: Should thoracic paravertebral blocks be used to prevent chronic postsurgical pain after breast cancer surgery? A systematic analysis of evidence in light of IMMPACT recommendations. Pain 2018; 159: 1955–71.
31. Capdevila X, Moulard S, Plasse C, et al.: Effectiveness of epidural analgesia, continuous surgical site analgesia, and patient-controlled analgesic morphine for postoperative pain management and hyperalgesia, rehabilitation, and health-related quality of life after open nephrectomy: a prospective, randomized, controlled study. Anesth Analg 2017; 124: 336–45.
32. Jendoubi A, Naceur IB, Bouzouita A, et al.: A comparison between intravenous lidocaine and ketamine on acute and chronic pain after open nephrectomy: a prospective, double-blind, randomized, placebo-controlled study. Saudi J Anaesth 2017; 11: 177–84.
33. Ren L, Peng L, Qin P, Min S: [Effects of two analgesic regimens on the postoperative analgesia and knee functional recovery after unilateral total knee arthroplasty–a randomized controlled trial]. Zhonghua wai ke za zhi [Chinese Journal of Surgery] 2015; 53: 522–7.
34. Macrinici GI, Murphy C, Christman L, et al.: Prospective, double-blind, randomized study to evaluate single-injection adductor canal nerve block versus femoral nerve block: postoperative functional outcomes after total knee arthroplasty. Reg Anesth Pain Med 2017; 42: 10–6.
35. McDonald DA, Deakin AH, Ellis BM, et al.: The technique of delivery of perioperative analgesia does not affect the rehabilitation or outcomes following total knee arthroplasty. Bone Joint J 2016; 98-b: 1189–96.
36. Ali A, Sundberg M, Hansson U, Malmvik J, Flivik G: Doubtful effect of continuous intraarticular analgesia after total knee arthroplasty: a randomized double-blind study of 200 patients. Acta Orthop 2015; 86: 373–7.
37. Wylde V, Lenguerrand E, Gooberman-Hill R, et al.: Effect of local anaesthetic infiltration on chronic postsurgical pain after total hip and knee replacement: the APEX randomised controlled trials. Pain 2015; 156: 1161–70.
38. Andersen KV, Nikolajsen L, Daugaard H, Andersen NT, Haraldsted V, Soballe K: Local infiltration analgesia is not improved by postoperative intra-articular bolus injections for pain after total hip arthroplasty. Acta Orthop 2015; 86: 647–53.
39. Villatte G, Engels E, Erivan R, et al.: Effect of local anaesthetic wound infiltration on acute pain and bleeding after primary total hip arthroplasty: the EDIPO randomised controlled study. Int Orthop 2016; 40: 2255–60.
40. Chou R, Gordon DB, de Leon-Casasola OA, et al.: Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016; 17: 131–57.

Corresponding author
Dr. med. Dominik Geil
Klinik für Anästhesiologie und Intensivmedizin
Universitätsklinikum Jena
Am Klinikum 1
07740 Jena, Germany
Dominik.Geil@med.uni-jena.de

► **Supplementary material**
For eReferences please refer to:
www.aerzteblatt-international.de/ref1519

Supplementary material to:

Chronified Pain Following Operative Procedures

The Place of Locoregional and Systemic Local Anesthetics

by Dominik Geil, Claudia Thomas, Annette Zimmer, and Winfried Meissner

Dtsch Arztebl Int 2019; 116: 261–66. DOI: 10.3238/arztebl.2019.0261

eReferences

- e1. Weibel S, Neubert K, Jelting Y, et al.: Incidence and severity of chronic pain after caesarean section: a systematic review with meta-analysis. Eur J Anaesthesiol 2016; 33: 853–65.
- e2. Statistisches Bundesamt: Krankenhausentbindungen nach Bundesländern: www.destatis.de/DE/PresseService/Presse/Pressemitteilungen/2018/09/PD18_349_231.html (last accessed on 03 March 2019).
- e3. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W: Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology 2013; 118: 934–44.
- e4. Chang YC, Liu CL, Liu TP, Yang PS, Chen MJ, Cheng SP: Effect of perioperative intravenous lidocaine infusion on acute and chronic pain after breast surgery: a meta-analysis of randomized controlled trials. Pain Pract 2017; 17: 336–43.
- e5. Bailey M, Corcoran T, Schug S, Toner A: Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety. Pain 2018; 159: 1696–704.
- e6. Herminghaus A, Wachowiak M, Wilhelm W, Gottschalk A, Eggert K, Gottschalk A: [Intravenous administration of lidocaine for perioperative analgesia. Review and recommendations for practical usage]. Anaesthesist 2011; 60: 152–60.