Local anesthetics: New insights into risks and benefits

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Conclusion and Discussion: Weighing risks and benefits of Regional Anaesthesia

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Introduction

During the past 30 years, regional anaesthesia has undergone dramatic changes in technique and indications, and has become a widely used method to provide intraoperative anaesthesia, and postoperative analgesia. A considerable base of scientific evidence has been achieved from which to estimate risks and benefits of regional anaesthesia, including the insight that the failure rate of regional anaesthesia in daily practice may be high.\(^1\) Evidence-based medicine seeks to combine these scientific results with pathophysiological knowledge and the needs of the individual patient to devise a judicious anaesthetic plan. This review seeks to address the question whether patient outcomes are sufficiently improved by regional anaesthesia to an extent that warrants its use as a routine perioperative method.

The benefits

In the past, the perceived ability of regional anaesthesia to provide excellent management of acute postoperative pain combined with a good safety profile was considered a sufficient reason in itself to perform regional anaesthesia. Indeed, many authors continue to appreciate the value of good perioperative pain therapy as such, even if it cannot be directly translated into improved overall long-term outcome.\(^2\) However, recent literature has advocated a more rigorous judgement of the value of regional anaesthesia. With the advent of improved general anaesthesia regimens and multimodal pain therapy, the superiority of regional anaesthesia in many types of surgery has receded to levels that may be statistically, but not clinically, significant.\(^3\) The benchmarks against which the efficacy of regional anaesthesia should be measured were summarized by Fischer (2010): optimal postoperative analgesia with a minimum of adverse effects, promotion of rehabilitative efforts, and improvement of long-term outcome including chronic pain.\(^4\) The problematic nature of these bars was highlighted in a recent editorial.\(^2\) Specifically, regional anaesthesia is but one, albeit important, therapeutic option during the perioperative course of an individual patient. In the optimal evidence-based situation, all patient- and procedure-related factors and interventions should be efficient in altering overall outcome. In an age where increasing numbers of patients are in fast-track discharge programs and
perioperative risk of major morbidity and mortality is low, respective benefits of regional anaesthesia become harder to discern.

Acute and Chronic Pain

Poorly managed acute postoperative pain is, in general, thought to be associated with the development of chronic pain. However, it is difficult to predict why certain patients go on to develop chronic pain while in others, pain resolves. Part of this risk is determined genetically. The respective concept is that of an “estimated heritability score”. In the case of acute pain, the risk “share” of genetic predisposition is between 22-55%. In contrast, the heritable component for the risk of developing persistent pain is higher, in the range of 55-68%. Such data clearly suggest a genetic predisposition for those who develop chronic pain following a precipitating incident. Pain which is difficult to control perioperatively may reflect greater sensitivity of patients based on genetic predisposition, with chronic pain as a logical consequence. Strict regimens of pain therapy may help to reduce chronic pain after prototypical high-risk, such as amputation. In the latter scenario, use of epidural anesthesia or peripheral nerve blocks may substantially reduce the rate of phantom limb pain, but the evidence-base is limited at this point. The prolonged use of peripheral sciatic nerve block for amputation was shown in recent reports to have a high success rate in preventing phantom limb pain. Potentially, future studies will make it possible to identify individuals at high risk of acute and chronic pain, and to tailor individual patient-specific treatment plans including the provision of regional anaesthesia, according to both type of surgery and type of patient. In patients at high risk of excessive pain perception undergoing major surgery, these treatment plans may include the combination of a sufficient regional blockade together with intravenous multimodal pain treatment (intravenous non-opiates, combined with, e.g., systemic ketamine, clonidine, or gabapentin / pregabaline). This would act to prevent the development of central sensitization via different pathways.
Peripheral Nerve Blocks

An exhaustive analysis by Liu and Wu examined the beneficial effects of regional anaesthesia when compared to systemic analgesia. In general, the authors found an average acute pain score with regional anaesthesia which was only marginally lower, and a lack of clear evidence showing improved long-term outcome. Despite the fact that many studies report statistically significant outcomes, a clear benefit in pain scores should only be assumed and taken as clinically relevant when the absolute pain intensity is different by 2 points on a 10-point scale, or pain differs by 33%. For specific surgeries, such as joint replacement, regional anaesthetic techniques such as single-shot or continuous peripheral nerve blocks are widely used, with an excellent safety profile and a substantial reduction in opioid administration. This was confirmed in recent meta-analyses and systematic reviews demonstrating superior analgesia, less opioid-induced side-effects and sleep disturbances, and facilitated rehabilitation when continuous nerve blocks were used for extremity surgery. The timepoint and definition of analgesic endpoint is important, as well. For example, the meta-analysis by Richman investigating continuous nerve blocks as compared to opioids showed that the mean VAS score was reduced from 3.7 to 1.7, on the verge of clinical significance. However, when maximal pain scores at breakthrough points were considered, the reduction was more pronounced, from 5.9 to 3.2. In the future, alternative blockades such as truncal blocks may replace epidural anaesthesia for some indications, but the evidence is insufficient at this moment. Early promising studies show that transversus abdominis plane block may promote short-term recovery after abdominal surgery, and may be an alternative to spinal morphine after caesarean section. Current literature regarding paravertebral blockade shows a trend towards equally effective analgesia as compared to the epidural route with potentially less adverse effects.

Epidural anaesthesia

Considering epidural anaesthesia for upper abdominal and thoracic surgery, Andreea found a beneficial effect of regional anaesthesia on development of chronic
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pain after open thoracotomy and breast cancer surgery but stated that in general, studies were of suboptimal quality and had included few patients. The combination of intraoperative epidural and multimodal analgesia has been found to prevent chronic pain after major abdominal surgery more effectively than multimodal analgesia alone. Moreover, patients undergoing major vascular surgery, and high-risk patients, have been found to experience less perioperative complications when general is combined with epidural anaesthesia, but the reported effect size is small. For example, epidural administration of local anaesthetics protects against postoperative ileus, but beneficial effects upon gastrointestinal motility have also been published regarding the intravenous administration of local anaesthetics. The same ambiguity also holds true for other outcomes. Whereas Liu did not observe a difference in quality of recovery, another meta-analysis by Poepping, including older studies, postulates that after upper abdominal and thoracic surgery, epidural anaesthesia decreases the risk of pulmonary complications. Notably, in the latter study, the incidence of pulmonary complications in patients receiving epidural anesthesia remained steady at 8% throughout the meta-analysis inclusion range, whereas the incidence in the systemic analgesia group decreased from 34% to 12%, most likely reflecting improved supportive perioperative care, and higher efficacy of multimodal systemic regimens. On a broader basis, it can be stated that the quality of multimodal intravenous regimens and perioperative care is improving, and it can be speculated that studies comparing the effects of epidural anaesthesia against optimal intravenous regimens will demonstrate beneficial effects on a much smaller scale. A recent Cochrane review failed to show a decrease in mortality in patients undergoing open abdominal aneurysm surgery, but the use of epidural analgesia reduced pain during the three first postoperative days (an arguable clinical benefit if only seen by itself), decreased postoperative ventilation time by half, and led to a reduction in postoperative myocardial infarction, acute respiratory failure, and gastrointestinal and renal complications. It can be summarized that epidural anesthesia and analgesia improve aspects of postoperative outcomes in selected patient subgroups. Contemporary medicine is facing two distinct but opposing trends. On one hand, evidence-based medicine relies on large-scale investigations
investigating aspects of patient care, and when large patient collectives are considered, the averaged effect size of epidural anaesthesia across all patients is small to modest. On the other hand, the future trend is that of personalized, individually tailored, medicine, based on, among others, the patient’s previous medical and pain history, and genetic background. This trend is certain to encompass the areas of perioperative and chronic pain medicine, and will lead to a further refinement of the indications for neuraxial blockade.

Regional Anaesthesia and Cancer Medicine

Whether regional anaesthesia has the potential to improve outcome in cancer patients has been the topic of intense discussion and research efforts ever since a retrospective study demonstrated survival benefits in patients subjected to perioperative paravertebral anaesthesia during mastectomy. Since then, some studies have confirmed this promising trend, others have failed to detect beneficial effects of regional anaesthesia, and some have found benefits only in specific patient subgroups. The mechanisms by which regional anesthesia may theoretically affect tumour progression are threefold. First, perioperative suppression of the surgical stress response by regional anaesthesia improves host defence, and may protect against circulating tumour cells. Second, opioids have arguably been linked to promote tumour growth in some experimental models and regional anaesthesia allows for dose-minimization of opiates, but it is unclear whether opiates clinically affect cancer recurrence. Third, local anesthetics present in the systemic circulation may directly limit viability of tumour cells, or sensitize them against chemotherapeutics. If the large-scale studies currently ongoing do find a clinically relevant effect of regional anaesthesia, it can be expected to be valid for certain types of tumour only, and depend on the molecular biological background of the specific malignancy.

Systemic Effects of Local Anaesthetics

Lastly, it should be mentioned that local anaesthetics have effects that reach beyond “just” nerve blockade and ensuing pain control. Among others, they have
been shown to beneficially affect the postoperative surgical stress response without impairing physiologic host response. Further, they have been shown to prevent hypercoagulable states in patients after major vascular and orthopaedic surgery without increasing the risk of bleeding. When compared to placebo, systemic administration of lidocaine has been reported to reduce opioid consumption and related side effects, decrease duration of ileus, and decrease length of hospital stay following abdominal surgery. Notably, these beneficial effects are observed after both open and laparoscopic surgery.

When comparing systemic lidocaine to epidural anesthesia as the conventional “gold standard” for major abdominal surgery, the results are less straightforward. Intravenous lidocaine started at the beginning of surgery has similar effects as epidural analgesia started within one hour after surgery regarding duration of ileus, pain, and length of hospital stay. However, in the latter study, initiation of the epidural was performed only after surgery, and was not standardized, even though other studies suggest that the main positive effect of epidural anesthesia and analgesia is attained intraoperatively. Another study compared intraoperative administration of thoracic epidural anesthesia, systemic lidocaine, or placebo. Postoperatively, all patients were connected to patient-controlled epidural analgesia (PCEA). Benefits on pain were short-lived after surgery as patients were allowed to administer boluses of epidural solution themselves. However, beneficial effects on duration of ileus, and the decrease in inflammatory mediators were more evident in patients who had received epidural than in patients who had received intravenous local anesthetics, and in both groups, functional outcome, but not length of hospital stay, was improved as compared to intraoperative placebo.

Adverse effects of intravenous lidocaine primarily stem from systemic toxicity, and most studies report plasma levels well below the toxic threshold of 5 µM. Signs of central nervous system toxicity are seldomly reported.

The systemic action of local anaesthetics is dependent on sufficient plasma levels usually reached during neuraxial block, peripheral nerve blockade, and intravenous administration. However, recent advances in the administration of ultrasound-guided regional anaesthesia have led to descriptions of block success in
the presence of dramatic reductions in the volume of administered local anaesthetic. Some reported volumes are less than 10% of the “traditional” volume administered when using nerve stimulation. Using very small volumes for peripheral nerve block is theoretically advantageous because of the decreased danger of systemic local anaesthetic toxicity, but at the same time, the systemic beneficial effects of regional anaesthesia, whose contribution is only beginning to be fully understood, will be lost because systemic absorption and resulting plasma levels are negligible.

In conclusion, beneficial effects of regional anaesthesia can be copied to a large extent by the systemic administration of local anesthetics. Considering the risk:benefit ratio, epidural anesthesia and analgesia should be considered in high risk patients, thoracotomy, and major upper abdominal and vascular surgery, whereas most cases of lower abdominal surgery and laparoscopic surgery can be adequately treated using multimodal analgesia.

The risks
When considering the risk aspect of regional anaesthesia, neurologic complications such as peripheral nerve injury or paralysis, and systemic complications such as local anaesthetic intoxication are the most commonly cited major adverse outcomes.

Permanent nerve injury
The incidence of perioperative peripheral nerve injuries has been assessed in a variety of studies and in general, retrospective studies show a much lower incidence than prospective studies. A summary of clinical studies by Brull et al. found a rate of neurologic complications of 0.04 % after neuraxial, and 3 % after peripheral regional anaesthesia, with the majority of neurologic deficits transient in nature. In a recent analysis of 1000 ultrasound-guided peripheral nerve blocks, the incidence of all-cause new-onset neurologic symptoms was 8.2%, with most cases unrelated to the block after thorough analysis. Since then, prospective data in 8,000 epidurals showed a complication rate for abscess formation of 0.1%. The Third National Audit Project of the Royal College of Anaesthetists reported
permanent disability or death from central nervous blockade between 0.7 and 1.8 per 100,000 procedures.\textsuperscript{39} The question whether regional anaesthesia is more dangerous in patients with pre-existing neurological disease has been controversially discussed.\textsuperscript{40} Current evidence suggests that symptomatic diabetic neuropathy may warrant a more careful weighing of the indication for regional anaesthesia, and may necessitate adaptation of technique, such as a decrease in local anaesthetic dose, and decreasing or omitting epinephrine from the injectate.\textsuperscript{40}

\textit{Systemic Toxicity}

Regional anaesthesia can further be complicated by systemic overdose of local anaesthetic. This potentially life-threatening adverse event occurs after inadvertent intra-arterial injection, intra-venous injection, or absorption following large-volume blocks.\textsuperscript{41} In the landmark study by Auroy and colleagues, seizures as indicators of systemic toxicity occurred in 1 / 10,000 patients undergoing epidural or spinal anaesthesia, and between 2 and 5 / 10,000 patients undergoing peripheral nerve blocks.\textsuperscript{42} Recently, ultrasound-guided peripheral regional anaesthesia was reported to cause seizures in 8 / 10,000 patients, with no incidences of cardiac arrest in a collective of more than 12,000 patients.\textsuperscript{43} Due to increased awareness and multiple safety steps such as aspiration, careful titration of the local anaesthetic, and the administration of test doses, the incidence of systemic toxicity is estimated to have declined by a factor of 25.\textsuperscript{41} In addition, intralipid has been introduced as a possible therapeutic adjunct for intoxication due to lipophilic local anaesthetics such as bupivacaine.\textsuperscript{44}

It should be briefly noted, however, that opiates as the main alternative substance for postoperative pain relief, can cause severe adverse effects as well, including respiratory depression and arrest. Together with anticoagulants and insulin, opiates are among the three most common substances to cause serious adverse drug events in hospitals.\textsuperscript{45}
**Other adverse events**

Several other potential adverse events need to be considered on a patient- and block-specific basis. Pneumothorax has been reported after several upper extremity nerve blocks, including interscalene, supraclavicular, and vertical infraclavicular.\(^4^6\) Vascular puncture can occur, with hematoma formation or, very rarely, pseudoaneurysm formation as sequelae.\(^4^6\) While this is perceived to be less of a problem in peripheral regional anesthesia, epidural hematoma formation may lead to compression of neural structures, and to permanent damage, with an incidence of 1:4000 – 1:6000 in the general surgical population, and less in obstetrical patients.\(^4^7\)\(^4^8\) Similarly, infection localized to the site of peripheral nerve block may be troublesome, but development of an epidural abscess may precipitate permanent neurologic dysfunction if occurring in the spinal canal.\(^4^9\) Moreover, excessive spread of local anaesthetic can lead to inadvertent blockade of nerves other than the target structure. Vocal cord paralysis can ensue due to recurrent laryngeal nerve block, and hemidiaphragmatic paresis can occur due to phrenic nerve block after interscalene or supraclavicular nerve block.\(^4^6\) These side-effects may potentially be avoided by using small volumes during ultrasound-guided nerve blockade.\(^3^5\) Again, these latter side-effects may be of limited clinical importance in healthy patients, but they may be detrimental in patients with specific co-morbidities, e.g., contralateral recurrent nerve palsy or severe chronic obstructive pulmonary disease, respectively.

**Weighing the risks and benefits**

At the moment, regional anaesthesia is undergoing a profound transition. The current trend is to reconsider and reappraise indications and contraindications for regional anaesthesia, often in the light of changing surgical techniques.\(^5^0\) One paradigmatic example is analgesia for total knee arthroplasty (TKA). Regional anaesthesia has been demonstrated to offer substantial benefits in the immediate perioperative period of TKA as compared to systemic analgesia, including superior pain control, reduced opioid consumption, and decreased opioid-related side-effects. In the middle term, ambulation and range of motion is improved in patients receiving regional anaesthesia groups, and rehabilitation goals are met faster.\(^5^1\) To
achieve this goal, some twenty years ago, it was considered good clinical practice to perform epidural analgesia or combined spinal-epidural anaesthesia and analgesia. However, epidural analgesia is frequently associated with pruritus, urinary retention and motor block, hindering optimal and early mobilization. Subsequent evidence demonstrated that a combined femoral / sciatic nerve block would provide the same degree of postoperative analgesia, but with a more favourable side-effect profile, especially concerning early mobilization. Currently, the two-block approach is undergoing scrutiny, and in many patients, continuous femoral nerve block (possibly combined with a single-shot sciatic nerve block) seems to provide satisfactory analgesia. Newer techniques such as saphenous nerve block seem even more tailor-made for analgesia following TKA. This nerve block provides analgesia for the anterior portion of the knee joint, while avoiding blockade of motor fibers such as those supplying the quadriceps muscle. In theory, mid-thigh saphenous block will combine the analgesia of a femoral nerve block but without the motor weakness potentially interfering with early rehabilitative efforts, providing targeted analgesia as peripherally as possible.

However, in the long term, outcome after one year following TKA is not as clear-cut. Whereas immediate postoperative benefits, including improved pain control and less adverse opioid-induced adverse effects can readily be detected in trials, functional patient outcome one year after surgery is not superior. With the current cost-driven trend to fast-track TKA patients, it becomes increasingly difficult to demonstrate outcomes such as reduced length of stay. It is debatable whether the facilitation of rehabilitation, which has been clearly demonstrated is a sufficient reason to perform regional anaesthesia if one-year functional outcome is not superior. The authors think that the combination of good perioperative pain therapy, decrease of opioid-related adverse events, and facilitated rehabilitation should be considered sufficient grounds to continue offering peripheral regional anaesthesia to patients undergoing TKA.
Future directions

Evolving research fields may alter the way we look at perioperative interventions, including regional anaesthesia. For example, epigenetics is concerned with the methylation of deoxyribonucleic acid (DNA), which determines gene expression. An increasing number of pathological conditions, among them persistence of experimental pain, has recently been linked to epigenetic irregularities. Interestingly, chronic opioid use in patients leads to increased DNA methylation correlating with increased pain, at least in part explaining opioid-induced hyperalgesia. The effect of clinically relevant concentrations of lidocaine has the opposing effect on methylation in vitro, i.e. de-methylation. Whether this molecular effect can be translated into strategies to decrease acute pain and prevent chronic pain needs to be determined at this point.

In parallel, the tools used to deliver Regional Anaesthesia are enhanced. One very prominent example is the new liposomal formulation of bupivacaine, which is entering the United States market, and may extend pain relief to 48-72 hours after a single bolus injection. The efficacy and safety of this treatment modality will undoubtedly be the subject of a large number of studies.

Conclusion

In conclusion, the question whether regional anaesthesia generally improves relevant indices of outcome in all patients has to be answered with no. Research has led to the reconsideration of indications and contraindications for regional anaesthesia in specific settings. The administration of regional anaesthesia necessitates a judicious weighing of risks and benefits. In general, the indications for epidural anaesthesia have decreased, and are limited to major upper abdominal and major vascular surgery, and thoracotomy. In addition, patients might benefit from regional anaesthesia on an individualized specific risk:benefit deliberation. It should be noted that when broad patient collectives are considered, the benefits of epidural anaesthesia are modest. Peripheral nerve blockade remains a mainstay of anaesthetic management for extremity surgery. At this time, there is insufficient evidence to ascribe a specific role to alternative blockades such as truncal blocks, but in the
future, they may replace epidural anaesthesia for some indications. Paravertebral anaesthesia may evolve into an alternative to epidural anaesthesia for thoracotomy. A substantial share of the alternative effects of regional anaesthesia on the immune system, postoperative ileus, and haemostasis are due to systemic absorption of local anaesthetics, and can be duplicated using intravenous administration of local anaesthetics. Low-volume peripheral nerve blocks may lack these beneficial effects because plasma levels are negligible. Multimodal analgesia has the potential to replace regional anaesthesia in many types of surgery. Regional anaesthesia continues to play a major role in perioperative medicine, but its role keeps getting more defined and less noncommittal.

Key messages
- Every regional blockade should be preceded by a weighing of potential risks and proven benefits, taking into account procedure- and patient-based factors.
- At least in part, many beneficial effects of Regional Anaesthesia can be duplicated by intravenous administration of local anaesthetics.
- Regional anaesthesia continues to play a major role in perioperative medicine, but its role keeps getting more defined and less noncommittal.

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