Risks and benefits of regional anesthesia in the perioperative setting

CHAPTER 8

General discussion and Summary

In this thesis we analyzed and investigated various risks and benefits of regional anesthesia in relation to different type of surgery and high-risk patient populations, chronic post-surgical pain, acute pain and anesthetic device characteristics.

We addressed the following research questions.

1. Does regional anesthesia improve outcome of peripheral vascular surgery as compared to general anesthesia?

In Chapter 2 we present an overview of current regional anesthesia techniques and strategies in a high-risk patient population undergoing peripheral bypass surgery. Our review showed that no superiority either of general, neuraxial, or local anesthesia or peripheral nerve blocks for this type of high-risk surgery can be demonstrated. At the same time we stated in this review that, even in the high risk patient population of peripheral bypass surgery, it is complicated to study the mode of anesthesia in relation to peri-operative morbidity and mortality. Surprisingly the present literature on this subject is scarce and the most recent analysis of the Cochrane collaboration[1] consisted only of 4 randomized controlled trials (RCT), analyzing studies from 1986-2007. Why is it then so difficult to perform RCT's in these peripheral bypass patients? Although the relative risk of mortality and morbidity in this patient population is relatively high, absolute numbers of patients involved in complications remain low[2] and thus a lot of patients have to be included in order to make evidence based recommendations. Inclusion of patients into RCT's in general is often complicated by the fact that they are excluded to participate based on age, co-morbidity and use of therapeutic anti-coagulation.[3, 4] Inclusion is further hampered by the fact that often the (elderly) patients are involved in other long term studies, which can make it unethical to include them in another study.

Nevertheless from our review we suggest that regional anesthesia supplemented by or in combination with either general anesthesia or monitored anesthesia care should be applied in view of a complete and comprehensive perioperative approach. This comprehensive perioperative approach includes not only combining anesthesia techniques. It is unlikely that one factor like regional anesthesia in itself may significantly change outcome.[5] A comprehensive perioperative approach and enhanced recovery program matching patient health risk factors, pre-operative risk assessment, anesthesia monitoring and selecting the most appropriate type of anesthesia in combination with the anticipated abdominal surgical procedure is more likely to change outcome and is currently only standard care in colorectal surgery. A comprehensive perioperative approach has shown to reduce overall morbidity rates and shortened the length of hospital stay in patients with colorectal surgery, without increasing readmission rates.[6] Regional anesthesia i.e. thoracic epidural analgesia is one of the major prerequisites of the enhanced recovery program.[5, 7] This fast track surgery/ accelerated or enhanced recovery program is at present incorporated in a lot of surgical pathways, like hernia

repair, thoracic and cardiac surgery, open aortic surgery and total hip and knee arthroplasty[5] , but should be extended to all procedures.

It should be noted that more focus at the individual patient and a tailored patient centered attitude is expected to significantly further improve the comprehensive perioperative approach. However, this may be difficult to prove as this inherently will lead to selection bias in studies, or a control group that may be more at risk for complications. Functional capacity of patients, whether dependent or not, may be suitable to select patients at risk for mortality and perioperative complications.[8] Subdivision of ASA-III patients based on the functional capacity, independent or not, was helpful selecting the more vulnerable patients.[8] For this group of vulnerable elderly patients at least additional depth of anesthesia and neuromuscular monitoring [9] is indicated in case of general anesthesia. Regional anesthesia alone or in combination with monitored anesthesia care or general anesthesia may offer an alternative. However, the choice of the anesthetic technique used, either regional or general, may be limited by the continuous use of perioperative anticoagulants.[10]

It is without any doubt that in future developments the comprehensive perioperative approach and enhanced recovery program will be further improved based on patient individual characteristics to allow a tailor made anesthetic treatment regime and that the individual genetic print of a patient due to results of pharmacogenetic studies[11] then definitely will be included and used to perform a risk analysis based on specific patient characteristics.

2. Does regional anesthesia reduce the incidence of chronic postsurgical pain in patients undergoing abdominal surgery?

In order to answer RQ2 a case-control study was performed in consecutive patients scheduled for elective open abdominal surgery who either received epidural anesthesia in combination with general anesthesia or general anesthesia alone. (Chapter 3). We report an overall incidence of chronic post-surgical pain (CPSP) of 25.7%, which is in accordance with that reported in literature.[12-15] We furthermore noted that patients with CPSP reported a significantly lower quality of life compared to patients without CPSP. After adjustment for prominent predictors of CPSP as there are not only age and gender but also pre-operative and acute postoperative pain, postoperative epidural analgesia was associated with a reduced incidence of CPSP after abdominal surgery. Studies on the effect of epidural anesthesia compared to general anesthesia with regard to the occurrence of CPSP are limited in number because the possibilities for randomized controlled trials (RCT's) are restricted as continuous epidural analgesia is superior to patient controlled intravenously administrated analgesia up to 72 hours.[16] Hence cohort studies are the second best option. The obvious absence of RCTs implies that it is extremely difficult to substantiate and demonstrate a causal relationship between epidural anesthesia and the occurrence of CPSP. On the other hand reproducible

observations based on various cohort studies can provide scientific evidence which is needed for recommendation.

In the field of acute postoperative pain several opportunities exist to elaborate a causal relationship between regional anesthesia and the occurrence of CPSP because several new complementary therapies are available. These therapies do allow the testing of clinically beneficial effect based on RCT's. Lidocaine intravenous[17, 18] and intraperitoneal infusion,[19] transverse abdominal plane (TAP) block[20, 21] and rectus sheath blocks[22] are in this respect, promising regional anesthetic techniques with a clinically beneficial effect based on positive RCT's . Whereas, at present, no superiority of these new complementary techniques in the field of acute pain is yet proven, RCT's are needed to compare them with established techniques as related to the occurrence of acute postoperative pain. In this respect, the focus should, however, not only be the acute postoperative pain. Clearly, future clinical studies are urgently needed to evaluate the impact of these regional anesthetic techniques and the development of CPSP.

3. Is there an additional value of regional anesthesia (paravertebral block) with respect to acute postoperative pain as compared to local wound infiltration?

Paravertebral block is one of the possibilities for regional anesthesia of the trunk. The majority of the studies on use of paravertebral blocks compare general anesthesia alone with regional anesthesia i.e. paravertebral block. Local wound infiltration is common clinical practice. It is therefore that we performed a randomized controlled clinical trial (RCT) in unilateral major breast cancer surgery patients receiving general anesthesia (GA) either in combination with continuous thoracic paravertebral block (GA-cPVB) or single shot (GA-sPVB) as compared to GA supplemented by local wound infiltration (GA-LWI) and acute postoperative pain. (Chapter 4) We hypothesized that improved acute postoperative pain relief would be achieved by using a continuous paravertebral block (GA-cPVB) compared to local wound infiltration (GA-LWI). The findings, however, were not in favor of our hypothesis as GA-cPVB and GA-LWI were equally effective in treatment of acute postoperative pain in these major unilateral breast cancer surgery patients. At present PVB is not recommended for routine use and minor breast cancer surgery.[23] The latter might also be the case in major oncological breast surgery as well.

It should be taken into account that our results are based on a relatively small study group and that GA-sPVB as one of the arms of this study, had to be stopped. Furthermore the conduct of this study was hampered by a slow inclusion rate, a low proportion of screened patients suitable for inclusion, and a high proportion of patients refusing participation in the study. Therefore we do not know whether our results may be extrapolated to a more general population. Consequently additional further RCT's are needed to demonstrate the effectiveness of GA-PVB versus GA-LWI focused at acute postoperative pain but also on the development of CPSP in patients scheduled for unilateral thoracic surgery.

4. What are the anatomical boundaries of the thoracic paravertebral space in view of the potential risks and benefits of the thoracic paravertebral block?

In Chapter 5 we describe the results of a human cadaver study on the thoracic paravertebral block. We determined the anatomical boundaries of TPVS in human thorax specimens and described the observed spread of fluid-like substances injected under ultrasound (US) guidance in the thoracic paravertebral space (TPVS). Our anatomical data show that TPVS communicated with all surrounding structures including the dorsal intercostal compartments, showing a segmental partition. Subdivision of TPVS in a sub-endothoracic and an extra-pleural compartment by the endothoracic fascia could not be confirmed. Injected plastic and dye were observed posteriorly to the costo-diaphragmatic recess and showed segmental intercostal spread.

Hence we conclude that the anatomical boundaries of the TPVS were relative borders as the TPVS communicated with all surrounding neurological structures.

Although TPVB is known for a long time new clinical insights and applications warrant a closer look into the anatomical details. The anatomical data as described in Chapter 5 of this thesis result in a better insight into the clinical effects and side-effects of the TPVB and afforded a glance behind the scenes regarding a possible mechanism of action: the clinical effects and side-effects of the TPVB are related to a direct penetration of local anesthetics into the surrounding neurological structures.

5. What is the impact of technical characteristics of catheters used in regional anesthesia on the performance in patients scheduled for elective surgery during normal daily practice under thoracic or lumbar epidural anesthesia?

In Chapters 6 and 7 we describe the results of clinical studies with respect to the incidence of paresthesia at introduction of a recently developed epidural catheter. In a pilot study (Chapter 6) the incidence of spontaneously reported paresthesia with a standard polyamide catheter was shown to be 21.3 % and 16.7 % with use of a combined polyurethane-polyamide catheter. Furthermore an overall intravascular cannulation incidence of 5 % and overall incidence of technical problems in 13.3% leading to premature catheter removal was noted in this pilot study. The results of the follow-up non-inferiority randomized controlled trial (Chapter 7) could partially confirm the pilot-study data. The findings of this RCT were at the end inconclusive in demonstrating non-inferiority of the polyurethane-polyamide catheter and showed significantly more flow problems postoperatively.

In the highly technical environment anesthesiologists are used to work, it is striking to see that the quality and impact of new industrial products like epidural catheters in a clinical setting are still not systematically investigated.

Anesthetic devices account for about 2 % of all new marked devices worldwide. At the same time these anesthetic devices do account for 30-40 % of all alerts.[24, 25] Whereas pharmacological drugs require extensive systematic clinical investigations and documentation on their effects and side-effects before approval the systematic testing and clinical data for clinical approval of anesthetic devices is extremely limited. [26] Only the so-called high-risk anesthetic devices are likely to have undergone extensive and systematic clinical testing before approval. High risk or Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.[27] These high risk anesthetic devices are evaluated by the U.S. Food and Drug Association (FDA) in the United States of America[27] and by Notified Bodies i.e. standard organizations supervised by Competent Authority of each country of the European Union.[28] It should be noted that based on a new Medical Device Directive of the European Community (2007/47/EC, (http://ec.europa.eu/health/medical-devices/files/revision_docs/ 2007-47-en_en.pdf)) which was became effective March 2010 stricter acceptance norms for devices are now required before approval and use in the clinic.[27] Manufacturers of high-risk anesthetic devices will now have to invest resources in conducting separate clinical trials for their devices as no longer new high-risk anesthetic devices will be CE approved just because of showing similarity with currently marketed products. The EC-directive obliges for clinical implementation of any new high risk anesthetic device (including epidural catheters) clinical studies and evidence based medicine. From our study we recommend approval of anesthetic devices based on careful study of inadvertent intravasal or dural cannulation, paresthesia rate, spontaneously and on questioning, catheter problem e.g. dislocation, kinking, disconnection, and problems with removal.

To improve patient care and to assist clinical decision making the concept of evidence based medicine was developed.[29] Then the highest level of evidence is established and based on systematic review and multiple randomized controlled trials (RCT). Nevertheless the question remains, even with the use of RCT's, if the results can be generalized to the wider community e.g. our daily practice.[3, 4, 30]

In this thesis we focused on the risks and benefits of regional anesthesia. As we earlier stated recommendations on procedures and devices on safety are difficult to make because of the low incidence of complications in the general population in combination with a wide diversity in type of anesthesia, minimal invasive surgery and contraindications. This implies the execution of very large time consuming expensive clinical studies, which are needed for optimal evidence based medicine and recommendations. As within this view RCT's are very complicated and difficult to perform other trial designs as an alternative[31-33] have been proposed. In view of this it is important to mention that a high risk filtered shed blood re-transfusion device is introduced in a number of hospitals in the Netherlands based on evidence collected in a prospective observational study.[34] In the scope of high risk anesthetic devices one must consider a

pragmatic rethinking of the design including RCT's needed for evidence based medicine. Hence, combining RCT's with a large observational cohort in a "cohort multiple randomized controlled trial" design would be a future interesting option.[35]

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