Local anaesthetic use in cancer surgery and disease recurrence: role of voltage-gated sodium channels?

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Recurrence of cancer after surgery remains a significant clinical problem. Interestingly, a number of retrospective studies have suggested that application of local anaesthetics during cancer surgery can be beneficial to patients in a number of ways. First, local anaesthetic use can reduce the chance of subsequent tumour recurrence.1–3 Secondly, postoperative pain can be suppressed, thereby minimizing the need to use opioid analgesics, which are known to be deleterious to the immune system.1–3 However, the mechanism(s) underlying these effects has not been clear. The discovery that cancer cells and tissues express functional voltage-gated sodium channels (VGSCs), well known to be a target of local anaesthetics, provides an opportunity to re-evaluate these phenomena.

Voltage-gated ion channel expression in cancer

VGSCs are functionally expressed de novo both in vitro and in vivo in a variety of carcinomas, including breast, cervical, colon, lung (small-cell, non-small-cell, and mesothelioma), skin, ovarian, and prostate cancers.4 In vitro, VGSC activity has been shown to enhance metastatic cell behaviours such as lateral motility and invasion.5,6 Cancer cells also express a range of other ion transporters, including voltage-gated potassium channels (VGPCs). The latter are commonly associated with apoptosis and growth.7 However, in relation to metastasis, VGPCs are thought to be down-regulated.5,8 Concomitant VGSC up-regulation and VGPC down-regulation would enable cancer cells to become ‘electrically excitable’ and, in turn, ‘hyperactive’ as the basis of their ‘aggressiveness’—this is the so-called ‘cellular excitability’ (‘CELEX’) hypothesis of metastatic progression.8

Beneficial effects of perioperative use of local anaesthetics on cancer and the possible role of VGSCs

It is well known clinically that breast cancer can reoccur after surgery (e.g. mastectomy), often within some 3 yr, and this is thought to be due to ‘showering’ of cancer cells during surgery and seeding in an immunosuppressed perioperative environment.9 The use of local anaesthetic and paravertebral analgesia were found to reduce cancer recurrence rates and improve survival of breast cancer patients in comparison with those treated with general anaesthetic and morphine.10 In such applications, apart from the preservation of the
immune system and the reduction in opioid requirement by regional anaesthesia/analgesia, local anaesthetic concentrations achieved in plasma by the regional technique may contribute to the improved survival. In a more recent meta-analysis, systemic administration of lidocaine during surgery was able to reduce postoperative pain and opioid requirements, supporting the role of lidocaine as an analgesic, anti-hyperalgesic, and anti-inflammatory agent. Parallel to these effects, VGSC mRNA and protein expression correlate with metastatic status in human breast cancer biopsies. Furthermore, the VGSC subtype (neonatal Nav1.5) expressed in the strongly metastatic human breast cancer MDA-MB-231 cells indeed was blocked by lidocaine with an IC50 of ~20 μM, within clinical range.

In a clinical study on prostate cancer, the use of local anaesthetic and epidural analgesia led to 57% lower recurrence rate after radical prostatectomy in comparison with general anaesthesia and morphine. However, another retrospective, single-centre study found no beneficial effect of combined general anaesthesia and epidural analgesia on the risk of cancer progression or improved survival after radical prostatectomy. At present, apart from some procedural differences, the reason(s) for this discrepancy is unclear and serves to demonstrate the complex pathobiology of cancer. There is already a wealth of in vitro evidence showing that VGSC activity promotes cellular motility and a range of other metastatic cell behaviours in prostate cancer. Direct evidence showing that blocking VGSC activity in primary tumour would suppress metastasis and prolong survival was demonstrated. However, it is not known if a local anaesthetic, like lidocaine, would inhibit prostate cancer motility by blocking VGSC activity. Interestingly, a recent study on strongly metastatic prostate cancer cells of rat showed that resveratrol, which may act at the same site as local anaesthetics, would indeed suppress cellular motility and invasiveness, most likely via VGSC (Nav1.7) inhibition (S.P.F., unpublished observations).

Melanoma patients enjoyed a 10 yr improved survival if given local anaesthetic over general anaesthetic during excision. A more recent study also suggested an association between spinal anaesthetic use and cancer outcome in melanoma patients after lymph-node dissection. In addition, these studies supported both the avoidan of general anaesthesia and the use of strong opioids. Functional VGSC expression was demonstrated earlier in human melanoma cells.

For aspects of colorectal cancer, also, there is evidence of some benefit of epidurals. Independently, it has been shown that functional VGSC expression promotes invasiveness in human colon cancer and is upstream to a key network of genes (including MAPK, Wnt, Ca2+ signalling, etc.) involved in this process.

Finally, we should note that further evidence should be available in some years following the ongoing large-scale prospective randomized multicentre trials on the effects of local anaesthetics on recurrence of various cancers (http://clinicaltrials.gov/show/NCT01204242).

**Fig 1 Proposed mechanism of local anaesthetic action to reduce metastasis recurrence and pain after surgery. Local anaesthetics work by inhibiting VGSC functioning. Such channels are known to be expressed in strongly metastatic cancer cells, where they function to promote cell behaviours such as motility and invasion. Local anaesthetics would block the VGSC activity during/after surgery and thus reduce the ability of the cancer cells to escape from the perioperative area and metastasize. This leads to a reduction in cell spread and the consequential increase in patient survival. In addition, local anaesthetic-induced VGSC blockage would suppress regional pain signalling. Together, these effects would lead to an overall improved survival rate and quality of life.**

**Further discussion, conclusions, and future perspectives**

We propose (i) that the use of local anaesthetics during and post-surgery would result in a beneficial reduction in the ability of the cancer cells to recur and metastasize and (ii) that inhibition of VGSC activity plays a significant role in this process. Thus, the VGSC blockage would suppress the motility and invasiveness of cancer cells and, in addition, reduce the signalling in the pain pathways associated with the surgery, the disease itself, or both (Fig. 1). Furthermore, the use of local anaesthetics may affect directly the local immune response to surgery, since lymphocytes also express VGSCs and their activity may promote their invasiveness as part of the inflammatory response.

At present, many other questions remain unanswered. For example, what are the relative contributions of other targets of local anaesthetics? Such non-VGSC-mediated action has been found to affect both cancer cell migration in vitro and metastasis in vivo. Local anaesthetics can also inhibit cancer cell proliferation in which VGSC activity would play no role. In addition, local anaesthetics can impact upon cells that do not express functional VGSCs. Local anaesthetics...
are also known to block VGPCs. Whether the reported antitumor effects of anaesthesia would involve VGPCs remains to be tested. However, it should be noted that VGPC blockade could ‘backfire’ by enhancing cellular invasiveness by promoting excitability.

The optimum plasma concentration of local anaesthetics to prevent recurrence is not known. Especially for the most direct technique of delivering local anaesthetic (i.e. i.v. infusion), the relevant safety guidelines (e.g. for lidocaine) have not been determined. Such guidelines should include dose-ranging regimens that are time-sensitive. Another key question is whether local anaesthetics should be given just during surgery or be continued after operation for the so-called ‘peri-operative decisive period’, which may be several days. It is also necessary to distinguish between the relative benefits of local anaesthetics use for (i) reducing cancer recurrence by VGSC blockade vs (ii) acting as an opioid-sparking agent. Future studies should aim to minimize opioid usage by using multimodal non-opioid adjuvants (e.g. non-steroidal anti-inflammatory drugs, α-2 adrenergic agonists) as part of the analgesic regimen. If opioids are still required, weak opioid agonists such as tramadol should be considered first. Finally, opioid use should be quantified, especially during the peri-operative decisive period.

Overall, in future, successful use of local anaesthetics in cancer surgery should take into account the nature and stage of cancer being operated on and both the type and mode(s) of action of the anaesthetic itself and any drug combination. The latter is essential for understanding how drugs given to cancer patients for controlling various side-effects of treatment might impact upon the cancer process itself.

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None declared.

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Chronic kidney disease: a gateway for perioperative medicine

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In this issue of the BJ A, Mases and colleagues1 on behalf of the Spanish ANESCARDIOCAT perioperative research group2 add important data to the expanding perioperative literature describing chronic kidney disease (CKD) as a consistent associate with postoperative morbidity. This post hoc observational study confirms the findings of a previous meta-analysis, showing an increased risk of perioperative major cardiovascular events in patients with estimated glomerular filtration rate (eGFR) < 45 ml min⁻¹ 1.73 m⁻².3 These data extend the perioperative CKD literature by assessing major adverse cardiac and cerebrovascular events (MACCE) in surgical populations other than vascular surgery,3 the chief focus of previous studies primarily due to the perceived higher event rate for MACCE in this population. At this juncture, it is worth bearing in mind that the ANESCARDIOCAT study defined MACCE without routine high-sensitivity troponin sampling—which may therefore underestimate the true magnitude of the association between CKD and cardiac ischaemic events.4 Indeed, the first cohort of the international VISION study (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study) suggests an association between postoperative troponin leak and degree of chronic renal dysfunction in ~15 000 patients.2 Both studies therefore reinforce the consistently negative impact of CKD on outcomes after non-cardiac surgery. Taken together with other recent studies, it is clear that even asymptomatic preoperative kidney impairment is associated with clinically significant increases in postoperative morbidity and mortality, as demonstrated in elective orthopaedic6 and major abdominal surgery.7 Thus, CKD defines a significant but substantial minority of patients who can be readily identified with real-time, objective, cheap, and prognostically important renal function tests that should be a key feature of every preoperative assessment.

By virtue of several creatinine-based prediction equations, the robust assessment of renal function is readily available (several web-based resources and apps are available; the calculators provided by the National Institute of Health National Kidney Disease Education Program are an excellent resource: http://www.nkdep.nih.gov). Of the purely creatinine-based equations, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula has emerged as the most robust calculator. CKD-EPI classifies fewer individuals as having CKD and is superior for quantifying the risk for mortality compared with the MDRD (Modification of Diet in Renal Disease) study equation across a broad range of populations.8 The measurement of cystatin C—which provides a measure of renal reserve that is independent of age, sex, and lean muscle mass—may further refine risk assessment in CKD.9 Since the categorization by the National Kidney Foundation of CKD into five stages of increasing severity (Table 1), CKD has consistently been associated—in a ‘dose-dependent’ fashion—with excess all-cause mortality and cardiovascular pathology in the general population of all healthcare systems/countries examined.10 UK-specific epidemiology makes similarly sobering reading. The NEOERICA (New Opportunities for Early Renal Intervention by Computerised Assessment) project found that the age-standardized prevalence of stage 3–5 CKD is 10.6% for females and 5.8% for males in the UK.11 The key repeated finding is that the majority of patients with CKD do not progress to end-stage renal failure, but rather sustain fatal cardiovascular complications prematurely. Most alarmingly, despite the clear association with excess morbidity and mortality, patients are frequently unaware of CKD as exemplified by the US REGARDS (REasons for Geographic And Racial Differences in Stroke) cohort study.12 In REGARDS, <10% of 3803 adults with coronary artery disease—and in routine contact with tertiary level medical providers—were aware of having CKD.

Impact of CKD on cardiovascular disease

Compelling epidemiological data show that CKD confers increased risk of cardiovascular morbidity and mortality, irrespective of age, gender, and ethnic group. While CKD in the UK population certainly associates with increased risk of hypertension, diabetes, and cardiovascular disease, an important recent study interrogating a large (1 268 029) patient cohort showed the true importance of recognizing CKD in relation to cardiovascular morbidity and mortality.13 In this cohort, the rate of myocardial infarction was lower in those with diabetes—without CKD—than in those with CKD without diabetes. The rate of incident myocardial infarction in people