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Regional Anesthesia And Breast Cancer Recurrence

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Abstract

Breast cancer is the most common type of cancer in women in the United States, and surgical resection is the definitive treatment. However, cancer recurrence and metastasis remains a concern for the lifetime of the patients affected. Therefore, much interest has been focused on how anesthetic technique may impact the rates of cancer recurrence and metastasis following breast cancer surgery. In this review, the potential for regional analgesia to reduce the recurrence rate of breast cancer post-operatively is discussed. Supporting evidence from multiple studies is presented, along with a discussion of potential areas of future research that is needed. At this time, there is no definitive answer regarding the optimal anesthetic technique to enhance patient outcomes after breast cancer surgery. However, ongoing research has the potential to enhance our understanding of how anesthetic technique may impact long-term breast cancer survival.

Introduction

In the field of anesthesia, practitioners are primarily concerned with the immediacy of their actions in the delivery of a safe and successful anesthetic. Anesthetic choice predominantly focuses on adequate sedation for the surgical procedure, perioperative pain control, respiratory and hemodynamic stability, as well as prevention of nausea and vomiting. When the patient's condition changes during the anesthetic, interventions are made to rapidly address those changes without much consideration for the potential long-term impacts of those interventions. Long-term effects of anesthetic choice on patient morbidity and mortality, which may not manifest for many years, are rarely considered in anesthetic plans, if at all. However, one area where

anesthetic choice may have a significant influence on long-term morbidity and mortality is the field of surgical oncology.

Perioperatively, several significant factors have been identified as having potential influence on cancer recurrence post-operatively, including physical manipulation of the tumor, immune system health of the patient, the stress response caused by the surgical intervention, and the choice of anesthetic technique (Snyder & Greenberg, 2010). For anesthetists, there has been a great deal of interest in the effects anesthetic technique may have on the recurrence rate of cancer after surgical tumor resection (Snyder & Greenberg, 2010). Of particular interest is the influence regional anesthesia may have on the long-term morbidity and mortality of patients undergoing surgical intervention for cancer treatment.

Anesthetic technique has been identified as having influence over immunosuppression, stress response, as well as tumor cell activity (Snyder & Greenberg, 2010). In the review by Snyder & Greenberg (2010) it was noted that all anesthetics (intravenous and inhalation) have the potential to decrease the immune response of the patient by inhibiting natural killer (NK) cell activity (Snyder & Greenberg, 2010). NK cells are noted as being one of the primary immune response cells in the control of cancer cells, which can often be released into circulation after tumor manipulation during surgery, leading to metastasis (Snyder & Greenberg, 2010). The stress response of acute surgical pain has also been identified as a causative factor in reducing NK cell activity and enhancing cancer cell proliferation intra-operatively (Snyder & Greenberg, 2010). Unfortunately, the use of opioids to treat acute pain has been implicated as a causative factor in suppressing NK cell activity (Snyder & Greenberg, 2010). Therefore, regional anesthesia and analgesia has been identified as a potential beneficial therapy to maintain immune

function during surgical resection of tumors, with the potential benefit of decreasing the risk of cancer recurrence and metastasis (Snyder & Greenberg, 2010).

In this literature review, evidence will be presented to illustrate the potential regional anesthesia may have on long-term morbidity and mortality in breast cancer patients who undergo surgical excision of their primary cancer. Specifically, the following question will be addressed; in patients undergoing mastectomies for treatment of breast cancer, how does regional anesthesia/analgesia compare to inhalation anesthesia with opioid analgesia in the post-operative recurrence rate of breast cancer? In addition, a discussion will be offered to illustrate why anesthetists should be open to plan their anesthetic choice in order to optimize the recovery potential in breast cancer patient.

Literature Review

Studies selected for inclusion in this review were found using the PubMed database with search terms of “cancer, regional anesthesia, epidural, paravertebral, breast cancer, recurrence, and metastasis”. Unfortunately, there were few articles of sufficient quality that directly applied to the treatment of breast cancer patients. Therefore, additional articles were selected that were similar in nature to the focus of this review. These articles were felt to lend support to the overall premise that there exists a potential benefit in the use of regional anesthesia in reducing cancer recurrence rates in breast cancer patients.

To date, there was only one study that closely addressed the question posed for this literature review (Exadaktylos, Buggy, Moriarty, Mascha, & Sessler, 2006). In this retrospective study, the effects of regional anesthesia and analgesia were examined to determine its influence on breast cancer recurrence and metastasis post-operatively (Exadaktylos et al., 2006). A total of 129 cases were examined from one hospital where patients underwent mastectomy with axillary

clearance for primary breast cancer treatment (Exadaktylos et al., 2006). All study participants received inhalation anesthesia for their procedures (Exadaktylos et al., 2006). The treatment groups consisted of 50 patients receiving regional analgesia (continuous paravertebral blockade), and 79 patients receiving opioid analgesia (Exadaktylos et al., 2006). The primary outcomes measured in the study were primary breast cancer recurrence and/or metastasis over 2-4 years post-operatively (Exadaktylos et al., 2006). Results from this study indicate a significant decrease in cancer recurrence or metastasis in those patients receiving regional analgesia compared to the opioid analgesia group (Exadaktylos et al., 2006). This pattern was evident at both 24 and 36 months follow-up (Exadaktylos et al., 2006).

While the results from this study were significant, the study design does raise some concerns in its interpretation. The study is a retrospective design, so the authors had no control over the patient selection criteria, or the specific anesthetic techniques utilized in the study. In addition, as the sample size was relatively small there is an increased chance that an effect was detected when one may not actually exist (Trochim & Donnelly, 2008). Also, the external validity of the results must be questioned, as the study was conducted at one facility and results may not be reflected by the larger population (Trochim & Donnelly, 2008). However, even with these concerns in mind the results from this study indicate a positive relationship between regional analgesia and improved patient outcomes in the surgical treatment of breast cancer.

Further evidence into the potential benefit of regional anesthesia in the treatment of breast cancer comes from the study of anesthetic technique on breast cancer cell activity *in vitro*. In one *in vitro* study, breast cancer cells were exposed to serum collected from patients undergoing mastectomy for breast cancer treatment (Deegan et al., 2009). Patients within the study were randomized into two treatment groups, those receiving paravertebral blockade with

Propofol anesthetic and those receiving opioid analgesia with Sevoflurane anesthetic (Deegan et al., 2009). The primary outcomes measured in this study were the extent of breast cancer cell proliferation, and the extent of cancer cell migration through a culture medium (Deegan et al., 2009). As an *in vitro* study, the goal was to determine how anesthetic technique might affect the ability of breast cancer cells to spread during surgical resection of a primary tumor, leading to recurrence or metastasis later in life (Deegan et al., 2009).

A total of 22 patients were recruited for the study, and were randomly assigned to the treatment groups (11 in each group) (Deegan et al., 2009). Serum was collected from study participants pre-operatively and 24 hours post-operatively (Deegan et al., 2009). Cultured breast cancer cells were exposed to the collected serum, allowed to culture for 24-48 hours, and then assessed for proliferation and migration (Deegan et al., 2009). Results from the analysis indicate that breast cancer cell proliferation was decreased in those patients receiving paravertebral blockade with Propofol compared to those receiving opioids with Sevoflurane (Deegan et al., 2009). The authors note there was no significant change in breast cancer cell migration between the two groups (Deegan et al., 2009).

Although this study had a small sample size, the overall design was robust in answering the questions posed by the authors. There was homogeneity between the two treatment groups, and the analysis of the results was clear and presented well. Although this was an *in vitro* study, it lends support to the idea that regional analgesia with Propofol anesthesia has the potential to decrease breast cancer recurrence or metastasis after surgical resection of breast cancer tumors by inhibiting cancer cell proliferation.

Another *in vitro* study examined the rate of apoptosis in cultured breast cancer cells when exposed to serum from patients undergoing mastectomy (Jaura, Flood, Gallagher, & Buggy,

2014). Serum was collected from 20 study participants (10 per group) who were given one of two anesthesia options for their surgical procedure. One group was given paravertebral blockade and Propofol anesthesia and the second group was given Sevoflurane anesthesia with morphine analgesia (Jaura et al., 2014). Serum was collected pre- and post-operatively, and cultured breast cancer cells were exposed to the subjects' serum, after which the extent of cancer cell apoptosis was measured (Jaura et al., 2014).

Results from the study demonstrated a higher rate of cancer cell apoptosis in the cultures exposed to serum from patients who received regional analgesia with Propofol anesthesia (Jaura et al., 2014). These results indicate that factors responsible for breast cancer cell elimination may be inhibited during surgery when Sevoflurane anesthesia with morphine analgesia is utilized (Jaura et al., 2014). Although these results are supportive for the use of regional analgesia with Propofol to reduce cancer recurrence in breast cancer surgery, it is clear this is a small *in vitro* study and extrapolation of these results to clinically relevant treatment choices must be viewed with caution.

A third *in vitro* study utilizing the same protocol as described above examined the effects of serum from patients undergoing mastectomy for resection of primary breast cancer on cultured NK cell activity (Buckley, McQuaid, Johnson, & Buggy, 2014). As noted above, NK cell activity is thought to be important in the elimination of cancer cells *in vivo* (Snyder & Greenberg, 2010). The two study groups were the same as above, paravertebral block with Propofol and Sevoflurane with morphine (Buckley et al., 2014). Cultured NK cells were exposed to serum from the study participants, and then monitored for cytotoxicity towards cultured cancer cells (Buckley et al., 2014).

Results from the study indicate that those patients exposed to Sevoflurane and morphine had impaired cytotoxicity of cultured NK cells towards cultured breast cancer cells (Buckley et al., 2014). The authors note that this result would seem to indicate a potential benefit in the use of paravertebral analgesia with Propofol anesthesia by maintaining NK cell activity (Buckley et al., 2014). In maintaining NK cell activity there is a potential to decrease the chances of breast cancer spread after mastectomy (Buckley et al., 2014). However, the authors also note that this is a small-scale pilot study with *in vitro* sampling, which should be viewed with caution when trying to extrapolate clinically relevant treatment choices (Buckley et al., 2014). Although the study is small scale, the design is robust in answering the question posed by the authors, and its results should be viewed as providing support to the use of regional analgesia in improving patient outcomes in the surgical treatment of breast cancer.

As there is a paucity of research articles directly addressing the question posed for this literature review, supporting evidence was sought for the use of regional anesthesia in reducing post-operative morbidity and mortality in the treatment of cancer. A retrospective meta-analysis was conducted by Weng et al. (2016) in an effort to exam the effects of neuraxial anesthesia, including epidural or spinal anesthesia, on morbidity and mortality following cancer surgery. After identifying 318 studies initially eligible for inclusion, 21 studies were ultimately selected for analysis (Weng et al., 2016). The goals of the meta-analysis were to examine the effects of neuraxial anesthesia, with or without general anesthesia, on the overall survival and recurrence free survival of patients after cancer surgery (Weng et al., 2016). The authors included studies published from 2004 to 2014, incorporating multiple different cancer types (Weng et al., 2016). Of these studies, 15 examined overall survival and 19 examined recurrence free survival (Weng

et al., 2016). Several studies selected for the meta-anlysis examined both overall and recurrence free survival, so were included in the analysis of each (Weng et al., 2016).

Results from the meta-analysis indicate a positive effect of neuraxial anesthesia on both overall survival, and recurrence free survival after cancer surgery when compared with general anesthesia alone (Weng et al., 2016). In addition, the authors noted that the positive influence of neuraxial anesthesia was significant even though the studies examined included multiple different cancer types (Weng et al., 2016). In an attempt to determine if specific cancers had an influence on the results identified by the primary analysis, the authors examined the influence of the types of cancers found more frequently in their literature search.

The effect of neuraxial technique on overall survival was analyzed in colorectal cancer (5 studies) and prostate cancer (3 studies) (Weng et al., 2016). In this sub-analysis there was a significant effect of neuraxial technique in colorectal cancers, but not in prostate cancer (Weng et al., 2016). The lack of significance in prostate cancer may have been due to the small number of studies used in the analysis. In comparison, the effect of neuraxial technique on recurrence free survival was analyzed in prostate cancer (7 cases) and ovarian cancer (3 cases) (Weng et al., 2016). In this analysis there was no significant effect of neuraxial technique on the recurrence of cancer in either group (Weng et al., 2016). The authors indicate that the strongest influence of neuraxial technique on cancer surgery is overall survival, but also note that there seems to be support for its use in decreasing cancer recurrence (Weng et al., 2016).

Overall, the study by Weng et al. (2016) provides strong support for the use of neuraxial anesthesia in the surgical treatment of cancer. Limitations of this analysis include a wide variety of cancer types examined to address the questions posed by the authors. A more robust analysis might include more studies with one specific cancer type. However, because of the limited

number of studies available, such an analysis was not possible. Interestingly, the authors' use of many different cancer types in this analysis lends support to the idea that there is a positive effect of neuraxial anesthesia on cancer surgery outcomes. Another weakness of the study was the lack of experimental design control inherent to retrospective analysis. The study by Weng et al. (2016) only examines the effects of presence or absence of neuraxial anesthesia during cancer surgery on their identified outcomes. It does not examine the influence of other variables such as inhalation anesthetics, opioids, and inflammation that may enhance the propensity for cancer recurrence or overall mortality. These uncontrolled for variables may confound a positive effect from neuraxial anesthesia, decreasing the authors' ability to detect a significant effect in their analysis. This is a common problem in retrospective studies, as the authors have no control over the study design of previous works. However, even with these limitations, the meta-analysis indicates a positive effect of neuraxial anesthesia in these cancer cases.

A closer examination of the studies utilized by Weng et al. (2016) can help to elucidate the potential impact neuraxial anesthesia may have on cancer surgery outcomes. One of the studies used by Weng et al. (2016) investigated the effects of epidural analgesia, compared to traditional analgesia, on overall and recurrent free survival of patients undergoing colectomy for colorectal cancer (Cummings, Xu, Cummings, & Cooper, 2012). The study was a retrospective population based cohort study, where cases within a large Medicare database were identified and selected based on a series of inclusion criteria (Cummings et al., 2012). The selection criteria was robust and identified over 40,000 cases that fulfilled their selection criteria, with more than 9,000 of those having an epidural at the time of surgery (Cummings et al., 2012).

Significant findings from the analysis of these cases indicated an increase in 5 year overall survival for those patients who received an epidural at the time of their surgery compared

to those who did not (Cummings et al., 2012). The authors do note that there was a difference in the population composition between the different study groups. Those patients receiving epidurals were slightly younger with lower comorbidity scores compared to the non-epidural group (Cummings et al., 2012). In addition, the epidural group had a higher likelihood to be white, males, married, and located in the Midwest region of the country (Cummings et al., 2012). After adjusting for patient characteristics, the analysis of the study continued to indicate an increased survival in the epidural use group (Cummings et al., 2012). In contrast to an increase in overall survival, there was no difference noted in the rates of colorectal cancer recurrence between the two groups studied (Cummings et al., 2012).

This study provides support in the use of epidural analgesia/anesthesia in reducing overall mortality in colorectal cancers. It utilized a robust database with a large sample size, and had a well designed inclusion/exclusion criteria. It was confounded somewhat in the differences noted in the two study groups identified (see above) and this does raise some doubts about the strength of the study conclusion. In addition, although the authors were able to utilize information from a large population database, they were limited in their lack of control over study design. The authors admit there may have been unintended bias in patient selection, or unaccounted for cofounding factors that may have influenced the results of the study (Cummings et al., 2012).

Another study utilized by Weng et al. (2016) examined the effect of neuraxial analgesia, as compared to opioid analgesia, on cancer recurrence in patients undergoing surgical resection of prostate cancer (Biki et al., 2008). In their retrospective analysis medical records were obtained from one facility where patients underwent radical prostatectomies (Biki et al., 2008). All patients received general anesthesia for their procedures, with patient selection based on the presence or absence of epidural placement for these procedures (Biki et al., 2008). A total of 225

cases were selected for analysis, with 102 of those cases receiving epidurals (Biki et al., 2008). Patients not receiving epidurals were given opioid analgesia post-operatively (Biki et al., 2008). The primary outcome measured in this analysis was recurrence of prostate cancer, based upon an elevation of prostate-specific antigen (Biki et al., 2008).

Results from the analysis indicate that recurrence-free survival was higher in those patients that received epidural analgesia when compared to those receiving opioid analgesia (Biki et al., 2008). Interestingly, the two study groups were not homogenous in their make-up, with the epidural group tending to have more complications, more comorbidities, and shorter surgeries (Biki et al., 2008). Despite the tendency to be sicker and have more surgical complications, the epidural group still demonstrated a 57% lower risk of cancer recurrence compared to the opioid group (Biki et al., 2008).

The results from this study further support the use of neuraxial analgesia in decreasing cancer recurrence in patients undergoing surgical resection of cancerous tumors. However, the sample size is relatively small (225 total cases), and the study only included cases from one facility (Biki et al., 2008). This study design may exhibit a decrease in external validity, and therefore may not provide results that are transferrable to different populations (Trochim & Donnelly, 2008). However, the results are promising and indicate a need for more robust testing of the efficacy of neuraxial analgesia in the reduction of cancer recurrence.

In addition to the use of regional techniques, other factors associated with anesthetic techniques and the recurrence rates of breast cancer have been explored in the literature. One study examined the influence of Propofol based anesthesia compared to Sevoflurane anesthesia on recurrence and overall survival of patients undergoing mastectomy for breast cancer (Lee, Kang, Kim, Kim, & Kim, 2016). In this retrospective study 325 cases were identified from one

treatment center where patients underwent mastectomy for breast cancer treatment (Lee et al., 2016). Cases were selected over a 24-month period, and categorized into the Propofol anesthetic group (173 cases) or the Sevoflurane anesthetic group (152 cases) (Lee et al., 2016). As it was a retrospective analysis, there was no control over adjunct medications given within those two groups (Lee et al., 2016). The primary outcomes measured in the study were recurrence free survival and overall survival within 5 years of follow-up (Lee et al., 2016).

Results from the study indicate there was no difference in overall survival within 5 years of mastectomy based on the anesthetic technique (Lee et al., 2016). However, cancer recurrence within 5 years of mastectomy was greater in the group that received Sevoflurane compared to those patients that received Propofol as their anesthetic (Lee et al., 2016). Results from this retrospective analysis seem to indicate a negative impact of Sevoflurane on recurrence free survival after surgical treatment for primary breast cancer.

Although a significant difference was noted between treatment groups, the results from this retrospective study must be viewed with caution. As the study participants were all selected from one facility the external validity of the results can be questioned (Trochim & Donnelly, 2008). In addition, as a retrospective study the authors had no control over the anesthetic technique utilized in their study groups. Therefore, confounding factors may have influenced the results of their analysis. An example of this was evident in the Propofol group, which showed higher usage of the opioid Remifentanil compared to the Sevoflurane group (Lee et al., 2016). It is not clear how Remifentanil might have influenced the recurrence rate of breast cancer, if at all.

Another study tried to determine the influence of intraoperative analgesics on the recurrence rates of breast cancer after mastectomy (Forget et al., 2010). In this retrospective analysis, the authors examined the use of sufentanil, ketamine, clonidine, and ketorolac on breast

cancer recurrence (Forget et al., 2010). There were 327 mastectomy cases identified from one facility, over a 5-year period, which were used for the analysis (Forget et al., 2010). There was no specific treatment group identified, but cases were analyzed for cancer recurrence based upon different choices of analgesic use perioperatively (Forget et al., 2010). Results from the analysis seem to indicate that those patients who received ketorolac before surgery had a lower rate of breast cancer recurrence compared to patients who did not receive ketorolac (Forget et al., 2010).

While the results from this analysis are encouraging, the retrospective nature of the analysis makes generalizing the results difficult. There was no control over the administration of analgesics in this study, and there are multiple factors that may confound the results found in this analysis. The authors do note that patients who received ketorolac tended to be younger, but also show that correcting for age still showed a positive effect of ketorolac use in reducing cancer recurrence (Forget et al., 2010). In addition to the retrospective nature of the study, the small sample size, and the use of one facility both act to reduce the external validity of the findings.

Discussion

The mechanisms that influence breast cancer occurrence, growth, and metastasis are complex, and vary from patient to patient (Snyder & Greenberg, 2010). Breast cancer pathophysiology has been linked to genetic predisposition, exposure to environmental triggering agents, and immune system impairment (Snyder & Greenberg, 2010). Because of this complexity, breast cancer recurrence after surgical resection remains a potential reality for patients long after surgical intervention to remove a primary tumor (Snyder & Greenberg, 2010). As members of the team of healthcare professionals involved in the care of breast cancer patients, anesthesia providers have a responsibility to provide a patient-centered anesthetic that will optimize patient outcomes postoperatively. To this end, anesthetists must educate

themselves about the potential benefits of different anesthetic techniques for breast cancer anesthesia.

From an anesthetists' point of view, the primary concern is always to provide a safe and effective anesthetic that allows for the surgical procedure required to remove the breast cancer. Achieving that goal can be done is a variety of ways, and in these cases the anesthetic choice may have significant impact on the long-term survival of breast cancer patients. Much of the debate regarding the ideal anesthetic revolves around limiting opioid use, and avoiding inhalation agents during breast cancer surgery as both of these agents have been implicated in higher recurrence rates of breast cancer postoperatively (Snyder & Greenberg, 2010).

Snyder & Greenberg (2010) present evidence suggesting opioid use, both acutely during the surgical procedure and chronically postoperatively, can suppress the immune system of breast cancer patients. This immune suppression is thought to allow for the proliferation of cancer cells that may be dislodged into circulation during surgical manipulation of the breast cancer tumor. Therefore, the use of regional anesthesia for perioperative pain control could potentially avoid the immune system suppression, and potentially decrease breast cancer recurrence in these patients.

Exadaktylos et al. (2006) were able to demonstrate the potential benefit of utilizing regional anesthesia in reducing breast cancer recurrence. When compared to anesthetics relying on opioid analgesia, regional anesthesia using paravertebral blocks resulted in decreased rates of breast cancer recurrence and metastasis after surgical intervention (Exadaktylos et al., 2006). This retrospective study has been a hallmark in efforts to promote regional anesthesia in the reduction of breast cancer recurrence postoperatively. However, as discussed above, the study has several limitations and does not address the influences of other factors present in the study,

such as the use of inhalation agents on cancer recurrence. In addition, although the study focused on regional anesthetic technique for pain management, all of the patients involved in the study received some form of opioid perioperatively. Therefore, it is not entirely clear if there would be an increased benefit in patient outcomes if an opioid-free anesthetic were to be utilized. Even with its limitations, the results from this study seem to indicate that there is a benefit to utilizing regional analgesia in reducing breast cancer recurrence, as compared to the use of opioids as the sole analgesia choice.

Further evidence supporting the use of regional anesthesia for pain control, and avoiding inhalation agents for anesthesia comes from three *in vitro* studies. These studies examined the effects of anesthetic technique on *in vitro* cancer cell proliferation and survival as a measure of the potential for breast cancer metastasis. All of these studies had similar study designs, where two treatment groups were utilized; patients who received regional anesthesia combined with Propofol sedation, and patients who received opioid analgesia with Sevoflurane anesthesia. In each study, cultured breast cancer cells were exposed to serum from the two treatment groups and the authors examined the effects based on the focus of their studies.

Deegan et al. (2009) examined overall breast cancer cell proliferation when exposed to serum from the two groups. The authors reported a decrease in breast cancer cell proliferation when cells were exposed to serum from patients receiving regional anesthesia combined with Propofol sedation (Deegan et al., 2009). Conclusions from this study seem to indicate that cancer cell proliferation may be enhanced in the opioid/Sevoflurane group due to an inhibition of immune factors present in the serum from those study participants (Deegan et al., 2009).

Jaura et al. (2014) examined rates of breast cancer cell apoptosis when exposed to serum from the two study groups. Results from this study found that breast cancer cells had higher

rates of apoptosis when exposed to serum from patients who received regional analgesia with Propofol sedation (Jaura et al., 2014). The authors implied that apoptosis was likely repressed in the opioid/Sevoflurane group through inhibition of serum mediated immune system factors.

Buckley et al. (2014) examined the level of NK cytotoxicity towards breast cancer cells when exposed to serum from the two study groups. Findings from this study described decreased levels of NK cell cytotoxicity towards breast cancer cells when exposed to serum from patients who received Sevoflurane with opioid analgesia (Buckley et al., 2014). These results were attributed to a direct inhibition of NK cell immune activity in the opioid/Sevoflurane group (Buckley et al., 2014).

Although these three reports were all *in vitro* studies, as a group they lend further support to the idea that regional anesthesia combined with Propofol sedation may maintain immune system efficacy in the control of cancer cell proliferation *in vivo*. These studies act together to indicate that providing an anesthetic with opioids and Sevoflurane has an inhibitory effect on serum bound immune factors and NK cell activity. This inhibitory tendency could allow for the proliferation of breast cancer cells during anesthesia for surgical resection of breast cancer. Therefore, the evidence indicates there is a potential for improved patient outcomes through the utilization of regional analgesia, combined with Propofol sedation in this patient population.

The potential of regional anesthesia in producing improved patient outcomes after cancer surgery has been demonstrated by several studies. Cummings et al. (2012) examined the effects of regional analgesia as compared to opioid analgesia in overall survival after colorectal cancer surgery. This study was conducted independent of anesthetic agent employed. Results from this study found an increase in overall survival postoperatively in those patients who received regional anesthesia as compared to those receiving opioid analgesia (Cummings et al., 2012).

Similarly, Biki et al. (2012) found that patients who received regional analgesia during surgical resection of prostate cancer had a decreased incidence of cancer recurrence postoperatively when compared to those who only received opioid analgesia, regardless of anesthesia agent use. In addition, a meta-analysis by Weng et al. (2016) demonstrated that there was an increase in overall survival, and a decrease in cancer recurrence for patients who received regional anesthesia for multiple cancer types. This benefit was present regardless of the type of anesthetic agent utilized, Propofol or inhalation agent (Weng et al., 2016).

An obvious limitation of the studies discussed above is the lack of work focused specifically on determining the effects of anesthetic agents on breast cancer recurrence postoperatively. Several of the studies reviewed above examined anesthetic technique, regional analgesia plus Propofol compared to opioid analgesia plus Sevoflurane, on patient outcomes. These analyses were not able to determine whether their findings were due to the anesthetic utilized or the type of analgesia selected. However, one study was found that specifically focused on the choice of anesthetic agent and breast cancer patient outcomes (Lee et al., 2016).

Lee et al. (2016) compared breast cancer recurrence and overall survival in patients who underwent anesthesia with Propofol anesthesia as compared to Sevoflurane anesthesia. Both study groups received opioid analgesia, and no regional analgesia was utilized (Lee et al., 2016). Findings from the analysis showed no difference in overall survival between the two groups, but recurrence of breast cancer 5 years after surgical intervention was lower in patients who received Propofol anesthesia (Lee et al., 2016). When these results are considered with the other studies listed above, the evidence becomes stronger that there is merit to the idea that limiting opioid use, utilizing regional analgesia, and avoiding Sevoflurane anesthesia has the potential to provide

for improved patient outcomes in patients undergoing surgical intervention for treatment of breast cancer.

Unfortunately, the overall evidence to date is not conclusive regarding the ideal anesthetic that would provide for the best patient outcomes after breast cancer surgery. Although there is supporting evidence for utilizing regional analgesia with Propofol sedation to reduce postoperative breast cancer recurrence, there is still much debate regarding the best practice in anesthetic management of these patients. The studies discussed above have several limitations, including small sample sizes, and a high proportion of retrospective studies that were included in this analysis. In addition, several of the studies were small *in vitro* experiments that may not be reflective of clinical outcomes. Therefore, in order to provide definitive evidence to guide best practice anesthesia management in breast cancer surgery, a large scale, multi-center, prospective randomized control trial is needed. Fortunately, one such trial is currently in progress (Sessler, Ben-Eliyahu, Mascha, Parat, & Buggy, 2008).

The study currently under investigation by Sessler et al. (2008) is focused on determining the effects of anesthetic technique and pain management on postoperative breast cancer recurrence and overall survival. This investigation is a robustly designed prospective randomized control study, conducted in several different medical facilities around the world (Sessler et al., 2008). The research protocol clearly identifies inclusion and exclusion criteria for study participants, with a target of 1100 patients enrolled over the course of the investigation (Sessler et al., 2008). The large sample size projected for the study affords an increased probability of avoiding a Type II error, and detecting a treatment effect if one exists (Trochim & Donnelly, 2008). In addition, the inclusion of patients from multiple medical facilities provides for adequate external validity in the analysis of their results (Trochim & Donnelly, 2008).

Protocols are also identified for how anesthetic treatment groups are to be managed, which provides for consistency in the delivery of anesthetic technique for study participants. The two treatment groups in the project are 1) regional analgesia using paravertebral blocks or thoracic epidurals combined with Propofol sedation, and 2) opioid analgesia combined with general anesthesia using Sevoflurane (Sessler et al., 2008). The authors clearly identify two hypotheses being tested; 1) patients receiving regional analgesia combined with Propofol sedation will show a reduction in postoperative breast cancer recurrence, as compared to patients receiving opioid analgesia with Sevoflurane anesthesia, and 2) overall patient mortality will be reduced in the regional analgesia with Propofol sedation group as compared to the opioid analgesia with Sevoflurane group (Sessler et al., 2008). It is hoped that once the results from this ongoing study are published, more clarity will be available for the optimal anesthetic technique in reducing postoperative morbidity and mortality for breast cancer patients.

In conclusion, the selection of a patient-specific anesthesia plan is the primary responsibility of every anesthetist, and a multitude of factors go into the planning of a safe and effective anesthetic. More often than not, anesthetists are concerned with the immediacy of their actions to address patient sedation, airway maintenance, and perioperative pain management. It is much less common for anesthetists to consider how their anesthetic choices may influence long-term morbidity and mortality for the patients they care for. As discussed in this review, the anesthetic management for patients undergoing surgical treatment for primary breast cancer may have lasting impacts on the cancer recurrence and overall survival of these patients.

The evidence gathered in this review lends support to the idea that inhalation agents and opioid use during breast cancer surgery both have the potential to promote breast cancer recurrences many years after surgical intervention. In comparison, evidence has been presented

indicating the potential for improved outcomes with the use of regional analgesia and Propofol sedation for patients undergoing surgical treatment of breast cancer. While the evidence is not definitive, and we are still awaiting results from more robust investigations, there is an argument to be made for utilizing this anesthetic technique in this patient population. The use of regional analgesia in breast cancer surgery is widely accepted in the anesthesia community as an appropriate choice for pain management. Propofol sedation is also universally accepted as an appropriate anesthetic choice. Therefore, in the development of an optimal anesthesia plan for breast cancer surgery, the anesthetist should weigh the potential costs and benefits of their anesthetic agents of choice.

There is an argument to be made that there is an increased risk of potential complications using a regional analgesia technique. Depending on the regional anesthetic technique utilized, complications from regional anesthesia used in breast cancer surgery can include injuries such as nerve damage, pneumothorax, or seizures and mortality in cases of local anesthetic toxicity (Macres, Moore, & Fishman, 2013). While these risks are a factor to be considered when using regional anesthesia, the risks are very low when administered by a skilled anesthetist (Macres et al., 2013). In comparison, the potential long-term benefit to the patient, reducing cancer recurrence and increasing survival, would seem to indicate an acceptance of the risks inherent to the use of regional analgesia.

When considering the choice of anesthetic agent, there are small differences in the risks to patients in choosing Propofol over Sevoflurane. One potential difference between anesthetic agents used in these surgical procedures is an increased risk of intra-operative awareness when using Propofol. Currently, there is no device utilized in the United States that allows for a reliable measure of adequate Propofol serum concentrations to ensure adequate sedation for

surgery. The best measure of adequate sedation when using Propofol is vigilant clinical monitoring by the anesthetist. In addition, there are brain-monitoring devices available that can be utilized to gauge overall sedation, but these do not provide a guarantee measure of depth of sedation. Regardless of the differences in overall risk profiles, the potential benefit to the patient in reducing postoperative morbidity and mortality seems to outweigh the potential risk of Propofol as the anesthetic choice.

The most important consideration in creating an anesthetic plan should always be focused on providing a safe and effective anesthetic. In the case for using regional analgesia and Propofol sedation in breast cancer surgery, the technique is both safe and effective for providing adequate analgesia and sedation. In addition, the evidence supports the potential long-term benefit for this anesthetic technique for breast cancer patients. By avoiding opioids and inhalation agents, anesthetists have the potential to significantly improve the surgical outcomes in this patient population. Until there is conclusive evidence that the use of regional anesthesia results in poorer patient outcomes in breast cancer surgery, it seems logical to err on the side of caution and utilize this technique whenever it is a reasonable choice.

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