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Review Article

Neuromuscular Blocking Agents and Cancer: A Narrative Review

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Objective. Neuromuscular blocking agents (NMBAs) are part of the three elements of general anaesthesia (sedation, analgesia, and muscle relaxation), which can relax muscles and facilitate intubation and surgery. It has been reported that cancer cells are prone to invasion or metastasis during surgery, but various anaesthetics are currently used in cancer resection, particularly NMBA, and the effects on cancer cell behavior are poorly understood. Guidelines for the correct application of NMBA in cancer surgery have not been reported; therefore, the aim of this paper is to explore the relationship between NMBA and cancer. *Methods*. Two investigators independently searched PubMed, Embase, the Cochrane Library, Web of Science, and CBM for articles of NMBA and cancer. *Results*. The available evidence suggests that cisatracurium may be more appropriate for use in anaesthesia for cancer surgery, while rocuronium deserves further attention, particularly for breast and gastric cancer surgery, and vecuronium is suitable for breast cancer and non-small-cell lung cancer, while it is used with caution in gastric cancer. Also, the relationship between NMBA (mivacurium, succinylcholine, gantacurium, and decamethonium bromide) and cancer is unclear and deserves further study. *Conclusion*. The effect of different NMBAs on cancer cells varies, and the effect of some NMBAs on cancer cells is unclear, and most of the current findings are only from in vitro studies, which need to be validated by further clinical studies in the future to better guide the clinical application of NMBAs.

1. Introduction

Cancer is a collective term for a number of diseases characterised by the growth of abnormal cells that divide out of control, infiltrate and destroy normal body tissues, and can spread throughout the body, making it one of the most common causes of death worldwide. With the development of modern molecular biology techniques and intensive research by scientists into the pathogenesis of cancer, there is a growing awareness that cancer is a multidimensional spatiotemporal "unity of ecology and evolution" pathological ecosystem that is highly complex, with onset and progression strongly influenced by the chemical and physical forces exerted by its surrounding microenvironment, and that manipulation of these "ecological" factors is increasingly attractive in the treatment of cancer [1, 2]. Therefore, in the context of anaesthesiology, it is of great significance to explore the relevance of different anaesthetic drugs to cancer progression, especially neuromuscular blocking agents (NMBAs), whose cancer-related studies are still scarce at present. In this paper, we will comprehensively review the published human and animal studies related to NMBA and summarise the effects of different NMBAs on cancer cells and their role in related

diseases, with a view to providing some reference for clinical application.

Cancer treatment generally uses chemotherapy, immunotherapy, radiotherapy, surgery, and other methods. Among them, surgery is one of the most effective and common methods for treating cancer, especially for early stage cancer, and its biggest advantage is that the tumor and the corresponding organ can be removed as a whole. When the tumor is at an early stage or the growing part has sufficient exposure space and sufficient resection scope, the choice of "radical surgery" offers a chance of clinical cure with complete resection. It is worth noting that general anaesthesia is often indispensable when cancer patients opt for surgical treatment, and therefore there is increasing interest in whether the various types of anaesthetic drugs currently applied have an effect on cancer cells, such as mutagenic potential, damage and metastatic capacity, and the growth of primary tumor cells [3, 4]. It has been reported that some general anaesthetic drugs can induce molecular biological changes such as cell proliferation, angiogenesis, and apoptosis through different physiological and pathological mechanisms [5], which is a strong indication that anaesthetic drugs may indeed interfere with tumor cells through certain mechanisms and thus affect the development and progression of cancer. The recent review article by Montejano and Jevtovic-Todorovic [6] provides a full summary of the effects of local anaesthetics, sedative anaesthetics, and opioids on the growth, differentiation, invasion, and metastasis of cancer cells. However, there is a lack of articles providing a comprehensive overview of the potential impact of NMBA on the development of cancer.

The purpose of the article is to review the latest news in the study of the effects of NMBA on cancer cells and to provide beneficial avenues for reducing the chance of undesired events, improving anaesthesia performance and patient safety. Through this article, you can learn about the role of NMBA in tumor treatment and how to choose an appropriate NMBA in general anaesthesia. Also, the article may also be regarded as a possible background for future research aimed at elucidating the complex interactions of biomolecular pathways between NMBA and some malignant tumors.

2. Methods

2.1. Literature Search Strategy. Two researchers (Rui Chen and Yan Sun) searched PubMed, Embase, the Cochrane Library, Web of Science, and CBM databases independently. Mesh and keywords used for the searches included "neuromuscular blocking agents" and "cancer." Furthermore, investigators scanned references of these articles to prevent missing articles.

2.2. Data Extraction Procedure. Two reviewers (Yufan Li and Xiaoke Dou) independently screened literature related to NMBA and cancer, extracted data, and cross-checked. The following literature will be excluded: (1) a duplicate article, (2) there are obvious errors in the data in the article, (3) titles or abstracts do not correspond to the subject of our review, (4) full-text articles not available, and (5) type of article as conference report, expert opinion, or comment.

3. Results

3.1. Non-Depolarizing NMBA

3.1.1. Rocuronium. Rocuronium bromide is one of the fastest acting non-depolarizing NMBAs available and is mainly excreted by the liver and to a lesser extent by the kidneys. Rocuronium bromide does not cause an increase in intraocular pressure or intracranial pressure and has no accumulative effect, making it suitable for anaesthetic use in patients with cranial hypertension and full stomach.

Treatment of MRC-5 fibroblasts with rocuronium reduces the expression of stromal cell-derived factor 1 (SDF-1), which has been identified as a contributing factor to cancer progression [7]. Rocuronium bromide promotes the proliferation, migration, and invasion of breast cancer cell line MDA-MB-231 [8]. Rocuronium can promote the growth, invasion, and migration of gastric cancer cells SGC7901 and BGC823 [9]. The rocuronium-induced neuromuscular blockade effect is similarly prolonged during liver resection in patients with hepatocellular carcinoma without preoperative hepatic impairment, but sugammadex reversal is effective [10]. Sugammadex, a potent antagonist of rocuronium bromide, is thought to promote recovery after surgery in cancer patients, but its effect on cancer cells has not been reported in studies, possibly because the drug's larger molecules do not enter cells [11].

In conclusion, the available evidence suggests that rocuronium bromide is associated with cancer cell invasion, adhesion, and migration, and the risk of postoperative recurrence and metastasis when applied in cancer patients is of concern, particularly in breast and gastric cancer patients undergoing surgery, and more in vitro, electronic, and clinical trials are needed to confirm these results in the future.

3.1.2. Cisatracurium. Cisatracurium, one of the ten isomers of atracurium, has the same muscle relaxation function and metabolism but has almost no side effects of histamine release and has slight cardiovascular effects. The study found that cisatracurium doses up to 64 times ED95 did not cause an increase in histamine concentration and cardiovascular effects in animals [12].

Cisatracurium inhibits the progression of OVCAR-3 cells by upregulating the expression of lincRNA-p21 activated by p53, which represses miR-181b expression [13]. Cisatracurium enhances TRAIL-induced apoptosis in gastric cancer cells via p53 signaling [14]. Cisatracurium can inhibit the proliferation, migration, and invasion of breast cancer MDA-MB-231 cells, and its mechanism is related to downregulation of the expression of intracellular miR-3174 [15]. Cisatracurium can stabilize hemodynamics during radical lung cancer surgery and reduce the incidence of postoperative cognitive dysfunction, and it is not closely related to dose [16]. Cisatracurium regulates the CXCR4/let-

7a-5p axis by inhibiting the TGF-β/SMAD2/3 signaling pathway, thereby inhibiting the survival, metastasis, and tumor growth of colorectal cancer [17]. In in vitro experiments, cisatracurium effectively inhibits the proliferation of colorectal HCT116 cells and induces apoptosis, at least by altering the p53-dependent apoptotic pathway [18]. Cisatracurium retards cell migration and invasion upon upregulation of p53 and inhibits the aggressiveness of colorectal cancer [19]. Cisatracurium has no significant effect on the malignant phenotype of gastric cancer cells SGC7901 and BGC823 with normal blood concentrations [9].

The available evidence suggests that cisatracurium is effective in inhibiting the proliferation and spread of cancer cells and its use in cancer patients is worth promoting; however, the above findings are yet to be validated in clinical trials and recommended by expert guidelines.

3.1.3. Atracurium. The advantage of atracurium is that it does not depend on liver and kidney metabolism and can be hydrolyzed by non-specific esterases and Hofmann elimination at physiological pH. However, large doses of atracurium can also lead to the production of histamine, which can lead to sharp changes in blood pressure and heart rate in patients, causing allergic reactions such as urticaria, severe hemodynamic fluctuations, and shock and bronchospasm in severe cases. Studies have found that atracurium besylate promotes astrocyte differentiation and depletes glioblastoma stem cells [20]. This means that atracurium is suitable for patients with glioblastoma. Atracurium gradually decreases cell proliferation in hepatoma HepG2 cells in a concentration-dependent manner [21]. Atracurium does not have any effect on heart rate and thus appears to be a better muscle relaxant in pheochromocytoma cases [22].

3.1.4. Mivacurium. Mivacurium is a newly developed benzylisoquinoline anaesthetic, which has been widely used in surgical anaesthesia due to its advantages of short action time and fast recovery. Its main benefits are as follows: good muscle relaxation effect and less nervous system toxicity, rapid dissolution by cholinesterase in plasma, no liver metabolism, no accumulation effect, etc. It is an ideal choice for short-term surgical patients who need tracheal intubation. The relationship between mivacurium chloride and tumors is unclear and deserves further study.

3.1.5. Vecuronium. Vecuronium bromide is a monoquaternary steroid, a derivative of pancuronium bromide, a medium-acting non-depolarizing muscle relaxant, used clinically mainly in combination with general anaesthetics for various procedures and endotracheal intubation. Different intravenous anaesthetics have an effect on the onset time of vecuronium. After induction with propofol, vecuronium can take effect faster, and after induction with thiopental sodium, it is slower.

It has been noted that vecuronium can affect the malignant phenotype of cancer cells at ordinary concentrations, and vecuronium can promote the adhesion of gastric cancer cells and has little effect on breast cancer cells [8, 9]. Vecuronium treatment also appears to reduce HGF expression at concentrations of 1.5 and 10 μg/ml, which is a key chemokine/cytokine produced by fibroblasts, thereby affecting tumor progression, but had no effect at the higher concentration of 15 μg/ml [7]. Vecuronium, which does not interfere with cardiovascular stability and has little or no histamine release, makes it one of the more appropriate non-depolarizing muscle relaxant for use during anaesthesia in patients with pheochromocytoma [23]. Vecuronium also induces GSC astrocyte differentiation in patients with glioblastoma multiforme [20]. Alport-leiomyomatosis syndrome is a very rare disease, and the available evidence suggests that vecuronium is safe and effective for anaesthesia in such patients [24]. An abnormally prolonged duration of action of vecuronium has been reported in female patients with neurofibromatosis, but there are no reports on the effect of vecuronium on the invasiveness of neurofibroma cells [25].

The effects of vecuronium on cancer cells are not conclusive, and more research is necessary to clarify the relationship between their roles.

3.1.6. Pancuronium. Pancuronium bromide has less effect on the cardiovascular system and does not cause the release of histamine. In adults, 1 to 2 mg of pancuronium bromide supplementation is required approximately every 45 minutes but is less common in prolonged surgery because at these doses pancuronium bromide appears to have a slight cumulative effect with repeated dosing. Side effects are rarely encountered with pancuronium. Patients with supratentorial tumors treated with pancuronium have a significantly greater increase in intracranial pressure and cardiovascular parameters [26]. Pancuronium bromide may not be suitable for anaesthesia in patients with this type of cancer.

3.1.7. Pipecuronium. Pipecuronium is a long-acting steroidal non-depolarizing muscle relaxant with no significant hemodynamic changes and no histamine production at clinical doses. Its muscle relaxant effect lasts for a long time and has little effect on circulation. Compared to pancuronium, pipecuronium provides significantly greater cardiovascular stability and less intracranial pressure rise during intubation and for the first 30 minutes thereafter [26]. In general anaesthesia, pipecuronium can be used as an anaesthetic-inducing muscle relaxant in patients with supratentorial tumors.

3.1.8. Gantacurium (AV430A). Gantacurium is a fast-acting, ultrashort-acting, non-depolarizing muscle relaxant for tracheal intubation and anaesthesia maintenance and for maintaining skeletal muscle relaxation during surgery and is antagonized by cysteine. Gantacurium has a slower onset of action than succinylcholine, and three times the dose of ED95 or even a larger dose is often required for satisfactory tracheal intubation. In this dose range, gantacurium may

Table 1: Summary of the main effects of NMBA on cancer.

Anaesthetics	Effects	Summary
Rocuronium	Rocuronium bromide promotes the proliferation, migration, and invasion of breast cancer cell line MDA-MB-231. Rocuronium can promote the growth, invasion, and migration of gastric cancer cells SGC7901 and BGC823.	Use with caution in patients with breast and stomach cancer
Cisatracurium	Cisatracurium enhances TRAIL-induced apoptosis in gastric cancer cells via p53 signaling. Cisatracurium inhibits proliferation, migration, and invasion of breast cancer MDA-MB-231 cells. Cisatracurium regulates the CXCR4/let-7a-5p axis by inhibiting the TGF-β/SMAD2/3 signaling pathway and inhibits colorectal cancer progression by altering the p53-dependent apoptotic pathway and delaying cell migration and invasion by upregulating p53, thereby inhibiting survival, metastasis, and tumor growth.	It is recommended for patients with ovarian, breast, lung, rectal, and gastric cancers
Atracurium	Atracurium besylate promotes astrocyte differentiation and depletes glioblastoma stem cells. Atracurium gradually decreases the cell proliferation of hepatoma HepG2 cells in a concentration-dependent manner.	Recommended for patients with glioblastoma and hepatocellular carcinoma
Vecuronium	Vecuronium bromide promotes adhesion of gastric cancer cells, inhibits proliferation and metastasis of non-small-cell lung cancer A549 cells, and has little effect on breast cancer cells.	Can be used in breast cancer and non-small-cell lung cancer, but used with caution in gastric cancer
Pancuronium	Patients with supratentorial tumors treated with pancuronium have significantly greater increases in intracranial pressure and cardiovascular parameters.	Use with caution in patients with supratentorial tumors
Pipecuronium	Pipecuronium provides significantly greater cardiovascular stability and less elevation of intracranial pressure during and for the first 30 minutes after intubation.	Suitable for use in patients with intracranial tumors
Tubocurarine	Tubocurarine blocks the stimulating effect of pilocarpine on prostate cancer proliferation. Tubocurarine blocks acetylcholine- (ACh-) induced currents (IACh) in pheochromocytoma cells (PC12 cells).	Suitable for use in patients with prostate cancer and pheochromocytoma

Note. The association of mivacurium, succinylcholine, gantacurium, and decamethonium bromide with tumor cell infiltration is unclear.

cause a significant release of histamine, which can lead to side effects such as a transient drop in arterial blood pressure and, in a few patients, flushing [27]. Considering the adverse effects of histamine release when gantacurium is applied at high doses, studies are currently underway to reduce histamine release while maintaining the potency, onset of action, and short duration of action of gantacurium, and CW002 and CW1759-50 may be the ideal muscle relaxants based on gantacurium at this point in time [27, 28]. However, there is a paucity of studies relating these muscle relaxants to tumor cell invasion, which may be a worthwhile frontier for research in the future.

3.1.9. Tubocurarine. The clearance of tubocurarine is less dependent on renal excretion, and it may be a good option for patients with renal failure [29]. After the administration of tubocurarine, there is a significant release of histamine and a significant decrease in blood pressure [30].

It has been shown that tubocurarine blocks the additional agonistic effect of carbachol on nicotinic cholinergic receptors in prostate cancer cells [31]. Low concentrations of (+)-tubocurarine blocks 5-HT3 receptor-mediated membrane currents in voltage-clamped clonal N1E-115 neuroblastoma cells [32]. The response of the mouse neuroblastoma cell line N1E-115 to iontophoretic application of acetylcholine consists of three phases, the initial rapid depolarization phase being blocked by tubocurarine [33]. Nicotinic acetylcholine receptors (nAChRs) are expressed on bronchial epithelial cells and non-small-cell lung cancer cells and are involved in cell growth regulation. Nicotine, the classic nAChR agonist, induces cell proliferation, while the nAChR antagonist, d-tubocurarine, induces cell death [34]. Thymosin alpha 1 (Talpha1), a 28 amino acid peptide, is a well-known immune system booster used to treat numerous diseases. The nAChR antagonist d-tubocurarine significantly antagonizes the inhibition effects induced by Talpha1 [35]. Tubocurarine can block acetylcholine- (ACh-) induced current (IACh) in PC12 cells [36]. The available evidence suggests that tubocurarine may have some inhibitory effect on tumor cell excitability.

3.2. Depolarizing NMBA

3.2.1. Succinylcholine. Low doses of succinylcholine are significantly more effective than cisatracurium for rapid tracheal intubation and can effectively suppress the cough reflex induced by tracheal intubation. The indexes such as the partial pressure of oxygen in the superior vena cava and the oxygen saturation are relatively stable, which is conducive to the balance of tissue oxygen supply and demand. Succinylcholine, a depolarizing neuromuscular blocking agent, is commonly used in medical protocols requiring short-term skeletal muscle paralysis, including rapid intubation in medical emergencies, due to its rapid onset of action and short half-life [37].

One investigator studied the effectiveness of succinylcholine in preventing the closed nerve reflex during transurethral resection of bladder tumors and found that succinylcholine was effective as an alternative to closed nerve blocks, and that none of the patients who were included in the observation receiving succinylcholine treatment developed closed nerve reflex [38]. However, no studies have been reported on whether succinylcholine has an effect on the invasiveness of cancer cells, meaning that the relationship between succinylcholine and cancer is unclear and deserves further study in the future.

3.2.2. Decamethonium Bromide. Decamethonium bromide belongs to the depolarizing NMBA, and the mechanism of muscarinic relaxation is similar to that of succinylcholine, which is mainly dependent on renal excretion. Because it is not easy to be metabolised in the body and often causes muscle pain and other adverse reactions, it is rarely used in the clinic. In a study of the effects of decamethonium bromide on skeletal muscle during chicken embryo development, it was found that decamethonium bromide induced oedema and high mortality in embryos, and that very few of the treated embryos survived for more than 16 days; furthermore, the degeneration of the abdominal, thoracic, and leg muscles was very pronounced, and the pathology sections showed a high degree of macrophage infiltration in the treated embryos; in short, decamethonium bromide has a blocking and inhibitory effect on the synthesis of the heavy chain of myosin in the developing avian embryo [39]. Due to the adverse effects of decamethonium bromide, its clinical use is low, its related reports are few, and in addition, its related tumor progression studies are hardly reported, even in animal studies.

4. Discussion and Conclusion

Cancer is one of the most frequent causes of death in countries around the world. Cancer treatment generally uses chemotherapy, immunotherapy, radiotherapy, surgery, and other methods. Anaesthesia is essential for cancer patients undergoing surgery, while NMBAs are one of the three main elements of general anaesthesia. Recently, people have begun to focus on whether there is a link between NMBA and cancer.

NMBAs play a role in intracellular pathways, can trigger biomolecular cascade reactions, and can participate in different physiological and pathophysiological functions such as cell proliferation, angiogenesis, and apoptosis [3–5]. Anaesthetic drugs, including NMBA, can act on molecular complexes, signaling networks, whole organelles, or other functional modules to regulate the cellular processes that influence the prognosis of cancer [40]. These findings may provide valuable information for the selection of appropriate anaesthetic drugs for cancer patients undergoing general anaesthesia. Finally, with regard to the possible effects of NMBA on cancer, the research results in the existing literature are very confusing, and it is difficult to draw accurate conclusions.

Studies have shown that rocuronium bromide promotes the growth, invasion, and migration of breast and gastric cancers. Cisatracurium can inhibit the proliferation, migration, and invasion of breast cancer cells and colorectal cancer cells, inhibit the progression of ovarian cancer cells,

and enhance the apoptosis of gastric cancer cells. Atracurium besylate can promote astrocyte differentiation and deplete glioblastoma stem cells and reduce the proliferation of liver cancer HepG2 cells. The relationship between NMBA (mivacurium and succinylcholine) and cancer is unclear and deserves further study. Vecuronium promotes gastric cancer cell adhesion, has little effect on breast cancer cells, and induces cell differentiation of GSC astrocytes in glioblastoma multiforme patients. Intracranial pressure and cardiovascular parameters are significantly increased in patients with supratentorial tumors treated with pancuronium. Tubocurarine blocks acetylcholine-induced currents in cancer cells. The main effects of NMBA on cancer are detailed in Table 1.

Most of these results now involve in vitro studies, so they should now be considered hypothesis generation. These anaesthesia mechanisms that regulate tumor behavior should be systematically analysed in animal models and clinical studies [41]. More importantly, the use of NMBA during surgery is transient, and many animal studies involve very high concentrations of NMBA and prolonged exposure; there is a lack of valid evidence on whether the routine use of NMBA in clinical anaesthesia has an effect on the prognosis of cancer patients, and more large samples and long follow-up studies are needed to demonstrate this.

Data Availability

No underlying data was collected or produced in this study.

Ethical Approval

An ethics statement is not applicable because this study is based exclusively on published literature.

Disclosure

The sponsor had no role in study design; collection, management, analysis, or interpretation of data; writing of the report; or the decision to submit the report for publication.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

CR and SY wrote the main manuscript text. LYF prepared the table. LYF and DXK searched the literature and selected the articles. DMS revised and polished the manuscript. SSJ and LY proposed research themes and coordinated work within the group. All authors have reviewed the manuscript and agreed on the journal to which the article should be submitted. CR, SY, and LYF contributed equally to this work.

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