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Recent Progress in the Study of Respiratory Complications Correlated with TACE for HCC

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Abstract

Due to the insidious clinical symptoms of early hepatocellular carcinoma (HCC), most of the patients diagnosed at intermediate-to-advanced stage HCC, and they lost the opportunity for curative treatment. Comprehensive interventional therapy plays an important role in prolonging the median survival of patients with intermediate-to-advanced stage HCC, among which transcatheter hepatic artery chemoembolization (TACE) is the most commonly used minimally invasive treatment. However, TACE may cause many postoperative complications such as liver function damage, biliary tract injury, upper gastrointestinal bleeding. Among them, TACE-related respiratory complications have been reported in a few articles, which are extremely rare but serious, and there are still many uncertainties about their occurrence mechanisms and risk factors. This article is aim to focus on the research progress of the respiratory complications of TACE, thus making progress on TACE-treatment aftercare.

Keywords

Hepatocellular Carcinoma, Transarterial Chemoembolization, Respiratory Complications

1. Introduction

Currently, primary liver cancer is the sixth most common malignant tumor and the third cause cancer-related death worldwide [1] [2] [3]. Due to insidious early symptoms of hepatocellular carcinoma (HCC) or impaired liver function, most patients are at the intermediate-to-advanced stage when diagnosed and miss the opportunity of surgical resection, so TACE is the main treatment for patients with intermediate-to-advanced stage HCC [4]-[9].

During the clinical application of transarterial chemoembolization (TACE), respiratory complications related to TACE occasionally occur, with a very low incidence of about 0.05% - 2.3%, but are seriously fatal, such as causing iodine oil pulmonary embolism, acute respiratory distress syndrome (ARDS), and acute lung injury (ALI).

With the increasing use of TACE in clinical practice, respiratory complications arouse attention by clinicians. At present, there are few reviews on TACE-related respiratory complications at home and abroad. This review is aim to synthesize the literature and research results and discuss the type, mechanisms and risk factors of respiratory complications of TACE in detail, with the aim of strengthening the clinical attention to respiratory complications and reducing the occurrence of such complications, thus improving the patients' postoperative living qualities.

2. TACE-Related Application and Types of Respiratory Complications

The angiogenesis theory involved in tumor growth was clarified by Judah Folkman, central arterialization of liver tumors is a multistep process that facilitates the transition of normal hepatic tissue from portal vein to hepatic artery, and finally to tumor [10] [11]. Transient slowing of blood flow through the tumor supplying arteries and supplying vessels can lead to a dramatic increase in intra-tumoral drug levels, and therefore transhepatic arterial injection of chemotherapy drugs in conjunction with embolization of tumor supplying vessels can substantially increase intra-tumoral drug levels compared to portal vein administration substantially increase intra-tumoral blood levels and lead to tumor ischaemic necrosis while reducing multiple side effects, making TACE a tumor-selective intervention [12]. Several randomized controlled trials and meta-analyses have demonstrated that TACE provides a greater survival benefit than conventional conservative treatment [4] [5] [6] [7] [13].

TACE-related respiratory complications are uncommon compared to other complications, but they are seriously fatal. According to the relevant literature and case reports, this review summarizes the respiratory complications that may occur after TACE as follows: iodine oil pulmonary embolism, acute respiratory distress syndrome (ARDS), infectious pneumonia, chemical pneumonia, lung abscess, pharmacological pneumonia, interstitial pneumonia, and lipoid pneumonia.

3. TACE-Related Mechanisms Causing Lung Injury

The mechanism of lung injury associated with TACE remains unclear, the most probably mechanism of lung injury is based on ectopic iodine oil embolism in lung tissue. Ruan [14] believed that lung injury pathogenesis after TACE was similar to that of fat embolism syndrome, and speculated that the inflammatory factors response to lung tissue were iodine oil, in which nitric oxide (NO),

phospholipase A2, free radicals and inflammatory cytokines (TNF-α, IL-1β and IL-10). Macrophages in the alveoli also played a crucial role in inducing nitric oxide synthase and promoting NO production in the lungs. Silvestri [15] reported an inflammatory response due to ethylated oils, confirming to some extent that the inflammatory response may also play an important role in initiating or maintaining pulmonary capillary leakage.

4. Causes of Respiratory Complications of TACE

Recently, domestic and foreign experts agreed that the respiratory complications associated with TACE were not caused by a single factor, but by a variety of factors affected by the synergistic effect, and some independent factors were common risk factors for different clinical pulmonary symptoms, which needed to be considered comprehensively for timely prevention and treatment. Possible factors are discussed as follows.

4.1. Postoperative Pain after TACE

It has been reported that nearly 75% of patients experienced severe pain after TACE treatment, and 93% of patients needed opioid analgesia within 12 hours after TACE therapy [16]. Pain led to a decrease ability to take deep breaths and caused severe cough, a decrease in the amplitude of diaphragm and intercostal muscle activity, and the postoperative change from spontaneous deep breathing to persistent shallow breathing, coupled with postoperative postural and activity restrictions, to a certain extent, results in insufficient pulmonary ventilation and the aggregation of intra-lung secretions. These factors rise up the possibility of postoperative lung infection.

4.2. Decreased Immune Function after TACE

Guan HT [17] showed that $CD4^+$ cells and $CD4^+/CD8^+$ ratio was significantly reduced and $CD8^+$ cells were increased in the early stage of patients after TACE, suggesting that the immune function of patients was impaired in the early stage after TACE treatment. Moreover, patients with HCC themselves were in a state of low immune function, so the organism is more susceptible to infections and complications of lung inflammation. Therefore, it is indispensable to adopt a standardized and reasonable pain management model for patients after TACE for HCC, and to improve the awareness of healthcare personnel on active intervention for postoperative pain, which can effectively prevent the occurrence of postoperative lung infection after TACE.

4.3. Liver Tumor Size and Location

Xu H *et al.* [18] found in a retrospective study that 11 patients with postoperative iodine-oil pulmonary embolism in 478 patients with TACE-treated HCC had tumors with blood supply and tumor diameters greater than 10 cm, and suggested that liver tumor diameter greater than 10 cm was one of the risk fac-

tors for iodine-oil pulmonary embolism. Therefore, the risk of iodine-oil pulmonary embolism should be noted when TACE was used to treat giant hepatocellular carcinoma (>10 cm), and the respiratory symptoms of patients should be closely monitored during and after surgery.

4.4. Hepatic Arteriovenous Fistula

Hepatic arteriovenous fistula was a defective vessel wall or formation of an abnormal vascular connection channel between the hepatic artery and the portal vein or hepatic vein. Hepatic arteriovenous fistulas were the main cause of iodine oil misembolization during TACE [19] [20], as well as one of the causes of postoperative complications of ARDS [21]. Kan reported that the route of iodine oil inflow into the pulmonary circulation for TACE was through hepatic arteriovenous fistulas and anastomoses with normal hepatic arteriovenous arteries [22]. Mechanisms of post-TACE complications due to hepatic arteriovenous fistulae HCC hepatic arteriovenous fistulae contributed to the shunting of infused iodine oil and chemotherapeutic agents into the lungs, resulting in chemical damage to the lungs. Previous reports have been found in patients with HCC combined with hepatic arteriovenous fistula [19] [20] [23] [24]. If a patient is at preoperative risk of hepatic arteriovenous fistula, further evaluation or angiography is recommended to detect the shunt. In addition, HCC patients with combined hepatic arteriovenous fistulae were reported by Fang [25]. At the time of angiography, the operator should carefully observe the liver for the presence of arteriovenous fistulae, and in the presence of hepatic arteriovenous fistulae, the degree of shunting can be reduced by ballooning the corresponding portal vein branches to block them [26]. Alternatively, the hepatic arteries can be treated by embolization of the hepatic arteries with a gelatine sponge, coils, or polyvinyl alcohol, which can significantly reduce the extent of shunting. The obvious arteriovenous shunt can be treated by embolization of the hepatic artery to prevent postoperative complications [27] [28] [29]. However, some subtle hepatic arteriovenous fistulas were difficult to detect by the naked eye during imaging [30]. Regardless of whether intrahepatic arteriovenous shunts were detected by CT and angiography, the operator should avoid the use of high doses of iodine oil and chemotherapeutic agents and closely monitor the patient for respiratory clinical symptoms when injecting iodine oil.

4.5. Embolization via the Inferior Phrenic Artery

The inferior diaphragmatic artery was the most common extrahepatic collateral vascular supply in HCC [31]. TACE via the inferior diaphragmatic artery increased the incidence of postoperative respiratory complications due to the presence of an arteriovenous shunt between the inferior diaphragmatic artery and the pulmonary arteries [32]. Iodinated oils or chemotherapeutic agents flow into the lungs through collateral circulation between the inferior diaphragmatic arteries and the pulmonary artery branches leading to lung tissue injury [33]

[34] [35]. Watanabe found that an increased incidence of respiratory complications in 40 cases of TACE via the inferior phrenic artery, with 14 cases of pleural effusion (35%), 11 cases of basal lung atelectasis (28%), and 1 case of haemoptysis (3%) [36]. After 44 transdiaphragmatic subarterial TACEs, CT showed a 70.5% rate of respiratory complications, with 23 cases of intrapulmonary iodine oil accumulation, 30 cases of pulmonary consolidation, and 18 cases of pleural effusion; the majority of these patients had only CT imaging manifestations and no clinical symptoms, with two of them experiencing the clinical symptoms of acute dyspnoea or haemoptysis [19]. In addition, Hatamaru reported a case of death from pulmonary embolism complicating TACE associated with embolization via the inferior phrenic artery [37]. Although TACE through the inferior phrenic artery has been adopted as a safe and effective treatment with rare serious complications, clinicians still need to take precautions to minimize complications.

4.6. Dosage of Adriamycin, Iodized Oil and Size of Microsphere Particle

Both conventional iodine oil-based TACE and drug-eluting microsphere TACE were used clinically in conjunction with chemotherapeutic agents to achieve optimal HCC treatment, with adriamycin being a commonly used chemotherapeutic agent in TACE. Adriamycin was an anthracycline that inhibited DNA topoisomerase II, and its main adverse effects were related to cardiotoxicity, with rare adverse effects on the lungs [38]. However, necrosis of pulmonary arterial endothelial cells and alveolar epithelial cells accompanied by peri-arterial oedema produced dose-dependent damage to lung tissue after receiving adriamycin pulmonary perfusion [39]. Aladdin and Khan reported cases of interstitial pneumonitis and acute diffuse lung injury caused by adriamycin after TACE [40] [41]. Also, adriamycin may be associated with mechanized pneumonia [42] [43]. Tajima was shown that the severity of respiratory complications increased with the injected dose of iodized oil and adriamycin [19]. Taken together, adriamycin plays a crucial role in lung tissue damage and requires accurate dosing of adriamycin by clinicans.

The mechanism of iodine-oil pulmonary embolism may cause by large-volume injection of iodine-oil embolism, which due to the increase in the pressure on the vessel wall by large-volume injection of iodine-oil embolism, leading to more iodine-oil passing through the vessel wall. Xu and Chung suggested that the amount of iodine-oil more than 20 mL injected in TACE may be an independent risk factor for iodine-oil pulmonary embolism after TACE and suggested that the safe iodine-oil dose for TACE may be 15 - 20 mL [18] [20]. Lin reported a positive correlation between the amount of iodinated oil injected during TACE and the duration of patient recovery ($r = 0.78$, $p = 0.013$) [44]. In addition, WU found that the safe iodine-oil dose to minimize the risk of iodine-oil pulmonary embolism is 14.5 mL or less, and multifactorial regression analyses showed that iodine oil dose can be used as a predictive factor for iodine oil pulmonary em-

bolism after TACE in patients with HCC [45]. Thus, larger prospective studies were needed to determine the optimal safe and effective dose. The dose of iodine oil used during TACE is determined by a variety of factors, the blood supply of the tumor, tumor size, physical condition, catheter location, liver function reserve [46] [47]. However, it is certain that the use of low-dose iodine oil chemoembolization as far as possible, under the premise of ensuring the therapeutic effect of TACE, can reduce the incidence of postoperative iodine oil pulmonary embolism. Therefore, the intraoperative dose of injected iodine oil should be strictly controlled, and if it exceeds 20 mL, it should be combined with the use of other embolization materials in order to reduce the incidence of postoperative iodine-oil pulmonary embolism and to prevent the further entry of iodine oil into the pulmonary circulation by the blood flow in the postoperative period, so as to avoid the further aggravation of iodine-oil pulmonary embolism.

The use of smaller diameter microspheres in DEB-TACE has been shown to be more efficacious than larger diameter microspheres in past studies [48] [49], because smaller microsphere particles were able to reach the tumor supplying arteries further and gave the tumor a higher blood concentration of the chemotherapeutic agent. However, Brown reported three cases of fatal pulmonary embolism due to the use of smaller microspheres (40 - 120 μm in diameter), suggesting that smaller particle diameters may increase the risk of pulmonary particle embolism [50]. The actual microsphere diameter threshold at which pulmonary embolism may occur has not yet been determined, and data from larger studies were needed to confirm the safety of microsphere particle size in relation to respiratory complications of TACE.

5. Diagnostic Imaging and Treatment of Severe Respiratory Complications after TACE

Accurate and reliable diagnosis is essential to achieve rapid and timely treatment of postoperative complications and to guide patient management, of which iodine oil pulmonary embolism and ARDS are serious respiratory complications after TACE with high mortality rates. Early respiratory symptoms in patients are usually non-specific, including cough, dyspnoea, difficult to breath and haemoptysis, and so on. In clinical practice, we mainly rely on imaging diagnosis, of which X-ray plain film and CT examination are more commonly used.

For patients with TACE-associated iodine-oil pulmonary embolism, chest CT is the main method to confirm the diagnosis, characteristically presenting as a new high-density iodine-oil deposition shadow in the lungs postoperatively, with or without peripheral interstitial exudates. Chest CT visually show the presence of iodine-oil retention in the lungs and the degree of iodine-oil deposition; in addition, CT pulmonary angiography (CTPA) is considered the diagnostic clinical gold standard in the diagnosis of pulmonary embolism, CT pulmonary angiography (CTPA) is considered the clinical gold standard for diagnosing pulmonary embolism, and its sensitivity and specificity were as high as nearly 100% [51]. The presence or absence of filling defects within the large and medium

branches of the pulmonary arteries, and clarified the extent and degree of thromboembolism.

TACE-related ARDS mostly occurs on the basis of iodine-oil pulmonary embolism, which meets the Berlin definition of ARDS [52]. X-rays mainly show diffuse exudation in both lungs in patches or asymmetrically. CT can be used as a substitute for or supplement to X-ray film and show high-density shadows with patchy images of iodine oil deposition in the lungs, and it can also show the presence of iodine oil deposits.

ARDS is significantly characterized by intractable hypoxaemia, and treatment includes supportive therapy and mechanical ventilation. The aim of mechanical ventilation is to provide oxygenation and ventilation while reducing the risk of ventilator-induced lung injury, mainly by lung-protective ventilation strategies: small tidal volume ventilation (LTVV), pressure-limiting ventilation, permissive hypercapnia (PHC), inverse ratio ventilation, and positive end-expiratory pressure (PEEP) [53]. The treatment of post-TACE ARDS caused by iodine-oil pulmonary embolism was on the basis of the experience of treating the fat embolism syndrome. In the post-TACE period, the treatment of post-TACE ARDS has been mainly based on fat embolism. The treatment of ARDS caused by iodine-oil pulmonary embolism is mainly based on the experience of fat embolism syndrome [54] [55]. Steroids improved respiratory symptoms in a few cases of post-TACE ARDS [41] [45] [56] [57]. Whether they had an impact on the prognosis and the outcome of the treatment needs to be further investigated.

6. Conclusion

Although respiratory complications of TACE in patients with HCC are rare, some serious respiratory complications such as pulmonary embolism, ARDS and other complications may even endanger their lives when they occur. Deepening the research, some risk factors for respiratory complications of TACE have also been confirmed. Therefore, it is important to assess the patient's overall health status and characteristics of HCC, to consider the possible risk factors of the patient in the comprehensive medical history, to avoid high-dose iodine oil and chemotherapy drugs and to closely observe the changes of the patient's blood oxygen saturation during surgery, and to assess the patient's clinical symptoms after surgery, so that the patient can be aware of potential respiratory complications after TACE at the earliest time point. If patients develop symptoms such as cough, haemoptysis, dyspnoea or shortness of breath after surgery, they should be alerted to the occurrence of respiratory complications, diagnosed in time, and accelerated for early management and treatment, in order to improve their prognostics.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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