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Research progress of bupivacaine liposomes in postoperative analgesia in patients undergoing abdominal surgery

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Abstract: Postoperative pain after abdominal surgery can cause both mental and physical trauma which directly affect the prognosis of patients. Effective postoperative analgesia can promote the recovery of gastrointestinal function and shorten the recovery process of patients. Bupivacaine liposomes are a new type of amide local anaesthesia developed in recent years using liposome technology for clinical application. Single dose injection can produce long-lasting analgesia for 72 hours, which is an important part of multimodal analgesia. Its application value has been widely validated in postoperative analgesia after total knee replacement, breast surgery and other surgical procedures. The article reviews the effects of bupivacaine liposomes on postoperative analgesia after abdominal surgery from the aspects of pharmacological properties, clinical application and safety.

Keywords: Abdominal surgery; Postoperative analgesia; Bupivacaine liposome; Pharmacokinetics; Pharmacodynamics

Pain is defined as an unpleasant sensory and emotional experience associated with potential tissue damage. Relevant reports indicate that over 80% of surgical patients experience postoperative pain, such as visceral pain and somatic pain. Among these, visceral pain typically lasts for a shorter duration with 6-12 hours, while somatic pain often persists for 2-3 days [1-2]. Postoperative pain is classified as acute pain, and inadequate control may lead to the development of chronic postoperative pain, significantly impairing patients' quality of life. Traditional analgesic agents for postoperative pain management in abdominal surgery patients include opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). However, extensive clinical practice in recent years has revealed limitations of opioids, such as excessive dosage, high incidence of nausea and vomiting, excessive sedation, and increased risk of postoperative respiratory depression [3]. NSAIDs like rofecoxib, while exerting anti-inflammatory and analgesic effects, may cause adverse reactions including gastric mucosal ulcers, bradycardia, and hypotension [4]. Epidural anesthesia has been reported to provide excellent analgesic efficacy, significantly reducing mental and physical burden in abdominal surgery patients. However, its clinical application is limited due to substantial impacts on hemodynamics [5]. With advances in understanding the mechanisms of postoperative pain, it has become evident that single analgesic agents is hard to achieve optimal efficacy across all pain types. Multimodal analgesia centered on local anesthetics is currently the preferred approach for effective postoperative analgesia in clinical practice [6]. Nevertheless, existing local anesthetics such as ropivacaine have a half-life of 162 minutes, with differential motor block and dose-dependent sensory block. They also exhibit strong toxicity to the central nervous system and heart, and excessive ropivacaine entering the bloodstream may induce ventricular arrhythmias [7-8]. Consequently, the development of novel long-acting local anesthetics has emerged as a key research objective. Bupivacaine liposome is a new type of local anesthetic prepared using liposomal technology. After local injection, it slowly releases bupivacaine over time. Compared to an equivalent dose of bupivacaine hydrochloride, it offers advantages such as longer time to peak concentration and lower peak plasma concentration, without the side effects associated with opioids or NSAIDs. It has been widely applied in multimodal analgesia management [9-10]. This study reviews the latest research progress on the application of liposomal bupivacaine in postoperative analgesia for patients undergoing abdominal surgery.

1 Bupivacaine liposomes

Liposomes are microvesicles that encapsulate active pharmaceutical ingredients within a lipid bilayer approximately 4 nm. They possess properties such as targetability, lymphatic tropism, sustained release, histocompatibility, and cell affinity, while also reducing drug toxicity and improving drug stability [11-12]. Bupivacaine is a small molecule substance that distributes rapidly after injection, exhibiting a strong analgesic effect but with a short duration of action. To prolong the analgesic time of bupivacaine, liposomes are clinically used to prepare bupivacaine sustained-release drug delivery systems [13]. Gabrielson *et al.* [14] prepared bupivacaine liposomes using the liposome active loading technology by ammonium sulfate gradient and found that maintaining the pH of the liposome

external environment at 5-5.5 resulted in the highest concentration of bupivacaine in the external aqueous phase of the liposome membrane without altering the ion or compound gradient in the internal aqueous phase of the liposomes. Bupivacaine liposomes feature sustained drug release. After local infiltration, plasma bupivacaine concentrations typically exhibit a biphasic pattern, with an initial peak occurring 2-4 hours after administration and a second peak appearing 21-36 hours later. Animal studies have shown that 24 hours after a single subcutaneous injection of bupivacaine liposomes in mice, the drug concentration at the injection site remains 20%-30% of the initial concentration, and residual drug concentrations can still be detected at the injection site at 48 hours [15]. Another study comparing the plasma concentrations of subcutaneous injections of bupivacaine hydrochloride and bupivacaine liposomes found that the time for 50% of bupivacaine liposomes to pass through a dialysis membrane was approximately 28 minutes, significantly longer than that of bupivacaine hydrochloride (7 minutes). The maximum plasma concentration of bupivacaine liposomes (0.12 mg/L) was significantly lower than that of bupivacaine hydrochloride (0.65 mg/L), and the steady-state plasma concentration of bupivacaine liposomes (0.1 mg/L) could be maintained for more than 7 hours, indicating a long analgesic duration and good safety profile [16]. Bupivacaine liposomes are prepared by encapsulating bupivacaine in the aqueous phase of liposomes using liposome technology; their active ingredient remains bupivacaine. They exert analgesic effects by blocking nerve impulse conduction through mechanisms such as stabilizing sodium ion channels on nerve cell membranes and reducing the firing rate of action potentials [17-18]. A study comparing the anesthetic effects of 0.4 mL of 5% bupivacaine liposomes and an equal volume of bupivacaine hydrochloride in a rat sciatic nerve block model found that the blocking effects of bupivacaine liposomes on sensory and motor nerves were 2.1 and 1.6 times those of bupivacaine hydrochloride, respectively, with a significantly longer anesthesia duration [(284.50±8.30) min] compared to bupivacaine hydrochloride [(90.50±8.00) min] [19]. Another multicenter, randomized, double-blind study showed that in patients undergoing elective hemorrhoidectomy, single local infiltration of bupivacaine liposomes at the postoperative incision resulted in a 72-hour cumulative pain score of 141 point and a total additional opioid use of 22.3 mg, both lower than those with bupivacaine hydrochloride (202 point and 29.1 mg, respectively).

2 The safety of bupivacaine liposomes

The efficacy of bupivacaine liposomes for postoperative analgesia depends on the concentration of bupivacaine at the injection site, while safety depends on the plasma concentration of bupivacaine. An animal experiment intraperitoneally injected 1.1% bupivacaine liposomes and bupivacaine hydrochloride of the same concentration into healthy mice, with median lethal doses (LD50) of 291 mg/kg and 61 mg/kg, respectively, indicating that bupivacaine liposomes have higher safety than bupivacaine hydrochloride [21]. The diameter of bupivacaine liposome multivesicular particles is only 10-30 μm. After local injection, their leakage rate is low, and they are not easily absorbed and metabolized by the blood circulatory system or lymphatic system. Increased local drug concentration can enhance the analgesic effects, while avoiding high plasma concentration in a short time, which can improve the safety of the central nervous system to a certain extent [22-23]. Foreign studies have injected 20 mL of 2% bupivacaine liposomes and 20 mL of 0.5% bupivacaine hydrochloride into healthy volunteers with no significant differences in baseline data, and found that even though the dose of bupivacaine liposomes was 4 times that of bupivacaine hydrochloride, the peak plasma concentrations in the two groups were basically consistent, indicating good safety of bupivacaine liposomes [24]. Another study applied bupivacaine liposomes to children aged 6-17 years undergoing cardiac or spinal surgery, and found that when bupivacaine liposomes were locally injected into the surgical incision at a dose of 4 mg/kg, the peak plasma concentrations were all below the plasma toxicity threshold of bupivacaine, and no serious adverse events occurred after surgery [25].

3 The role of bupivacaine liposomes in postoperative analgesia for patients undergoing abdominal surgery

Effective postoperative analgesia management in patients undergoing abdominal surgery reduces the incidence of central and peripheral pain sensitization, lowers the risk of lower extremity venous thrombosis, and promotes patient recovery [26]. Bupivacaine liposomes can provide sustained analgesia for 72 hours, and some domestic and international disease diagnosis and treatment guidelines recommend the application of bupivacaine liposomes in postoperative multimodal analgesia for abdominal surgery.

3.1 Postoperative analgesia for major abdominal surgery

Scholars have found that a single postoperative injection of bupivacaine liposomes can significantly reduce the total consumption of opioids within 48 hours after surgery in a randomized controlled trial on postoperative pain after laparoscopic hepatectomy, while also lowering patients' rest and active pain scores and the risk of gastrointestinal reactions such as nausea and vomiting [27]. Turan *et al.* [28] conducted a study in which patients undergoing major abdominal surgery were randomly assigned at a 1:1 ratio into an epidural analgesia group and a transversus abdominis plane block with liposomal bupivacaine group. The results showed that the postoperative rest pain scores in the transversus abdominis plane block with liposomal bupivacaine group,were significantly lower than those in the epidural analgesia group [estimated difference: 0.09 (95% *CI*: -0.12-0.30, $P < 0.05$)], but there was no significant difference in opioid consumption between the two groups within 3 days after surgery [estimated difference: 1.37 (95% *CI*: 1.05-1.79), $P = 0.754$]. Thus, bupivacaine liposomes have a significant advantage in reducing postoperative pain in patients undergoing major abdominal surgery. Another study conducted a retrospective analysis of clinical data from adult patients undergoing major

lower abdominal surgery under general anesthesia and found that patients who received postoperative infiltration analgesia with bupivacaine liposomes had significantly lower time-weighted pain scores from 0 to 72 hours after surgery compared with those who received patient-controlled epidural opioid analgesia [29]. Bupivacaine liposomes mainly exert analgesic effects through transversus abdominis plane block, which can reduce the dosage of systemic anesthetic analgesics such as opioids. Under the premise of using bupivacaine liposomes for postoperative analgesia, observing the dosage of opioids can reflect the analgesic effect of bupivacaine liposomes to a certain extent. A study included patients undergoing hepatectomy who received transversus abdominis plane block (with bupivacaine liposomes as the main drug), with postoperative pain scores as the primary outcome and total opioid consumption as the secondary outcome. It was found that compared with patients without transversus abdominis plane block, those with transversus abdominis plane block had significantly lower pain scores at 24 hours after surgery, and the oral morphine dosage was significantly reduced [30].

3.2 Postoperative analgesia for gynecological surgery

When abdominal surgery is necessary due to the patient's condition, under the premise of not compromising surgical efficacy, a small incision can reduce intestinal interference. However, there remains a high risk of postoperative pain. Studies have confirmed that for patients undergoing laparoscopic hysterectomy, the application of bupivacaine liposome for transversus abdominis plane block under ultrasound guidance at the end of surgery can effectively reduce postoperative pain scores and decrease the consumption of opioid analgesics [31]. In addition to pain directly induced by the small incision, gynecological laparoscopic surgery may also cause postoperative abdominal distension and bilateral costal pain due to acute peritoneal distension caused by CO_2 pneumoperitoneum, as well as small peritoneal vessel tearing and carbonic acid stimulation on the peritoneal surface [32]. A study injected a mixture of 5 mL bupivacaine liposome, 1:200,000 epinephrine, and 5 mL normal saline sequentially into the transversus abdominis plane preoperatively in patients undergoing robot-assisted laparoscopic hysterectomy. Compared with the control group (5 mL bupivacaine hydrochloride + 1:200,000 epinephrine + 5 mL normal saline), the bupivacaine liposome group significantly reduced postoperative pain scores and shortened the length of hospital stay [33]. Results from a randomized double-blind placebo-controlled trial showed that the pain scores in the intervention group (postoperative local injection of bupivacaine liposome) at 12 h, 24 h, and 48 h postoperatively (3 points, 3.5 points, and 2.75 points, respectively) were all lower than those in the control group (postoperative local injection of bupivacaine hydrochloride) (3.5 points, 5 points, and 4 points, respectively). Additionally, the rate of additional opioid administration in the intervention group from 24 to 48 h postoperatively was also lower than that in the control group [34].

3.3 Postoperative analgesia for gastrointestinal surgery

In a prospective randomized controlled trial comparing bupivacaine liposome with standard bupivacaine alone in colorectal cancer resection, the observation group received a block with 40 mL of 0.125% standard bupivacaine + 20 mL of bupivacaine liposome postoperatively, while the control group received a block with 60 mL of 0.125% standard bupivacaine. The results showed that the 48-hour postoperative pain score in the observation group was significantly lower than that in the control group, with less opioid consumption. However, there was no significant difference in the incidence of adverse drug reactions between the two groups. This indicates that bupivacaine liposome has a good postoperative analgesic effect and good safety [35].

Other studies evaluated the application value of bupivacaine liposome in postoperative analgesia for colorectal cancer based on postoperative pain scores and the incidence of intestinal obstruction. They found that in the adjusted time trend analysis, postoperative analgesia with bupivacaine liposome significantly reduced postoperative pain scores, reduced the risk of postoperative intestinal obstruction to a certain extent, and shortened the length of hospital stay. Clinically, bupivacaine liposome may be considered for inclusion in the standard transversus abdominis plane block protocol [36]. A study included 179 patients undergoing laparoscopic Roux-en-Y gastric bypass surgery, of whom 89 received postoperative injection of bupivacaine liposome and 90 received an equal volume of bupivacaine. The results showed that the proportion of patients taking analgesics in the bupivacaine liposome group on postoperative days 2–4 was significantly lower than that in the bupivacaine group, and the pain scores from 0 to 72 hours postoperatively were significantly lower in the bupivacaine liposome group, indicating a good analgesic effect of postoperative bupivacaine liposome injection in laparoscopic Roux-en-Y gastric bypass surgery [37]. Another study used a non-anesthetic approach for postoperative analgesia in laparoscopic sleeve gastrectomy and evaluated the postoperative analgesic effect of bupivacaine liposome based on pain scores and postoperative morphine consumption. The results showed that the pain scores immediately after surgery and at 12 hours postoperatively in the bupivacaine liposome group were lower than those in the control group (tramadol intervention), with less postoperative morphine consumption than the control group, indicating a definite analgesic effect [38].

3.4 Postoperative analgesia for other abdominal surgeries

A study performed rectus sheath block and local infiltration anesthesia in patients undergoing laparoscopic appendectomy. The results showed that patients who received rectus sheath block with bupivacaine liposome had lower initial pain scores and average pain scores at 72 hours postoperatively than those who received local infiltration anesthesia with ropivacaine, indicating that bupivacaine liposome has high application value in preoperative anesthesia and postoperative analgesia [39]. A study on postoperative pain management in laparoscopic abdominal liposuction

showed that the frequency and dosage of intravenous morphine use in patients who received bupivacaine liposome for postoperative analgesia were significantly lower than those in patients not using bupivacaine liposome for analgesia, suggesting that bupivacaine liposome can effectively alleviate postoperative pain and reduce patient discomfort [40]. Lu Jianguo *et al.* [41] compared the analgesic effects of bupivacaine liposome and bupivacaine hydrochloride after intercostal nerve block in single-port thoracoscopic lung surgery. They found that the time to first use of analgesics postoperatively and cumulative opioid consumption at 72 hours postoperatively in the bupivacaine liposome group were both less than those in the bupivacaine hydrochloride group, indicating that bupivacaine liposome can effectively reduce postoperative pain in patients undergoing single-port lung surgery.

A study applied bupivacaine liposome in open umbilical hernia repair. The weighted pain scores at 120 hours and 10 days postoperatively were both ≤2.3 points, which were lower than the median pain score (5.5 points), and no other adverse events occurred postoperatively, suggesting that bupivacaine liposome has good analgesic effect and safety [42].

4 Summary

Bupivacaine liposome is a novel amide local anesthetic that employs liposome technology to encapsulate the drug within a lipid bilayer, thereby achieving long-acting sustained release. It is characterized by stable release, stable blood concentration, and prolonged analgesic duration, making it an ideal local anesthetic for postoperative analgesia in abdominal surgeries such as major abdominal surgery, gynecological surgery, gastrointestinal surgery, and laparoscopic appendectomy. Additionally, it provides new insights for postoperative analgesia in other surgical procedures. However, currently, the approved indications of bupivacaine liposome in China are limited to local infiltration analgesia and nerve block, resulting in a restricted scope of application. Its efficacy and safety still require confirmation through more high-quality clinical studies.

Conflict of interest None

Reference

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·研究进展·

布比卡因脂质体在腹部手术患者术后镇痛中应用的研究进展

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摘要：腹部手术术后疼痛可造成患者精神、躯体双重创伤，直接影响患者预后转归。而术后有效镇痛可促进患者胃肠功能恢复，缩短患者痊愈进程。布比卡因脂质体是近年来临床采用脂质体技术制备的新型酰胺类局部麻醉药，单剂量注射可产生72 h长效镇痛，是多模式镇痛的重要组成部分，其在全膝关节置换术、乳腺手术等多种外科手术术后镇痛中的应用价值已得到广泛证实。本文将从药理学特性、临床应用、安全性等方面综述布比卡因脂质体在腹部手术术后镇痛的应用效果。

关键词：腹部手术；术后镇痛；布比卡因脂质体；药代动力学；药效动力学

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Abstract: Postoperative pain after abdominal surgery can cause both mental and physical trauma which directly affect the prognosis of patients. Effective postoperative analgesia can promote the recovery of gastrointestinal function and shorten the recovery process of patients. Bupivacaine liposomes are a new type of amide local anaesthesia developed in recent years using liposome technology for clinical application. Single dose injection can produce long-lasting analgesia for 72 hours, which is an important part of multimodal analgesia. Its application value has been widely validated in postoperative analgesia after total knee replacement, breast surgery and other surgical procedures. The article reviews the effects of bupivacaine liposomes on postoperative analgesia after abdominal surgery from the aspects of pharmacological properties, clinical application and safety.

Keywords: Abdominal surgery; Postoperative analgesia; Bupivacaine liposome; Pharmacokinetics; Pharmacodynamics

疼痛是潜在组织损伤引起的不愉快情感和感觉经历，相关报道显示，80%以上的外科手术患者会出现术后疼痛，如内脏痛、躯体痛，其中内脏痛持续时间较短，为6~12 h，而躯体痛往往持续2~3 d[1-2]。术后疼痛属于急性伤害性疼痛，若未得到有效控制，易演变成术后慢性疼痛，严重影响患者生存质量。腹部手术患者术后疼痛的传统药物包括阿片类药物、非甾体抗炎药，但近年来大量临床实践发现，阿片类药物在镇痛过程中存在用量过大、恶心呕吐发生率高、过度镇静，术后呼吸抑制发生风险高等缺点[3]；非甾体抗炎药如罗非昔布，在发挥抗炎止痛作用的同时可能会产生胃黏膜溃疡、心动过缓、低血压等副作用[4]。报道发现硬膜外麻醉镇痛效果良好，可显著减轻腹部手术患者精神和体力负担，但对血流动力学的影响较大，临床应用受限[5]。随着对术后疼痛机制研究的深入，发现单一镇痛药物很难对所有类型的疼痛产生良好的镇痛作用，以局麻药为主的多模式镇痛是目前临床进行术后有效镇痛的首选[6]。然而，现有局麻药罗哌卡因半衰期达162 min，且运动阻滞分离、感觉阻滞具有剂量依赖性，对中枢神经系统、心脏的毒性较强，过量罗哌卡因进入血液循环可能会导致室性心律失常[7-8]，因此开发新型长效局麻药物成为新的研究目标。布比卡因脂质体是采用脂质体技术制备而成的新型局麻药，局部注射后随着时间推移缓慢释放布比卡因，与等剂量盐酸布比卡因比较，具有达峰时间长、血药峰浓度低等优势，且没有阿片类药物、非甾体抗炎药的副作用，已广泛应用于多模式镇痛管理[9-10]。本研究综述布比卡因脂质体在腹部手术患者

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术后镇痛中应用的最新研究进展。

1 布比卡因脂质体

脂质体是将药物有效成分包封于厚度约为 4 nm 的类脂质双分子层内的微型泡囊，具有靶向性、淋巴定向性、缓释性、组织相容性与细胞亲和性，同时可降低药物毒性，提高药物稳定性[11-12]。布比卡因为小分子物质，注射后分布较快，镇痛作用强但作用时间短，为了延长布比卡因镇痛时间，临床将脂质体用于制备布比卡因缓释给药系统[13]。Gabrielson 等[14]研究采用硫酸铵梯度主动载药法制备布比卡因脂质体，发现将脂质体外环境 pH 维持在 5~5.5 时，脂质体膜外水相中布比卡因浓度最高，且未改变脂质体内水相离子或化合物梯度。布比卡因脂质体具有可持续释放药物的特点，局部浸润后血浆布比卡因浓度多表现为双向模式，即给药 2~4 h 后出现初始峰值，21~36 h 后出现第二个峰值。有研究通过动物实验发现，于小鼠体内单次皮下注射布比卡因脂质体 24 h 后，注射部位药物浓度为初始药物浓度的 20%~30%，且 48 h 仍可在注射部位检测到部分药物浓度[15]；也有研究通过对比盐酸布比卡因、布比卡因脂质体皮下注射后血药浓度发现，50% 布比卡因脂质体通过透析膜的时间约为 28 min，较盐酸布比卡因（7 min）明显延长，最大血药浓度 0.12 mg/L 明显低于盐酸布比卡因 0.65 mg/L，且布比卡因脂质体稳态血药浓度 0.1 mg/L 可维持 7 h 以上，可见布比卡因脂质体镇痛时间长，且安全性良好[16]。布比卡因脂质体是利用脂质体技术将布比卡因包封于脂质体水相而制取，其有效成分仍为布比卡因，主要通过稳定神经细胞膜上钠离子通道、降低动作电位增射速率等作用机制阻滞神经冲动传导，发挥镇痛作用[17-18]。有研究比较 0.4 mL 的 5% 布比卡因脂质体与等量盐酸布比卡因在大鼠坐骨神经阻滞实验中的麻醉效果，发现布比卡因脂质体对感觉神经、运动神经的阻滞作用分别是盐酸布比卡因的 2.1 倍、1.6 倍，且麻醉时间[(284.50±8.30)min]明显长于盐酸布比卡因[(90.50±8.00) min][19]。另一项多中心、随机双盲研究显示，择期行痔疮切除术的患者术后切口局部单次浸润布比卡因脂质体，术后 72 h 累积疼痛评分为 141 分，追加阿片类药物使用总量 22.3 mg，均低于盐酸布比卡因（202 分、29.1 mg）[20]。

2 布比卡因脂质体的安全性

布比卡因脂质体用于术后镇痛的疗效取决于注射部位布比卡因浓度，而安全性则取决于血浆内布比卡因浓度。一项动物实验将 1.1% 的布比卡因脂质体与同浓度的盐酸布比卡因分别注入健康小鼠腹腔，其半数致死量分别为 291 mg/kg、61 mg/kg，可见布比卡因脂质体安全性高于盐酸布比卡因[21]。布比卡因脂质体多囊粒直径仅为 10~30 μm，局部注射后，其渗漏率较低，且不易被血液循环系统、淋巴系统吸收代谢，局部药物浓度升高后可增强镇痛效果，同时避免短时间内高血浆浓度，一定程度上可增加中枢神经系统安全性[22-23]。国外有研究分别于基线资料无明显差异的健康志愿者体内注射 20 mL 的 2% 布比卡因脂质体、20 mL 的 0.5 % 盐酸布比卡因，发现即使布比卡因脂质体剂量是盐酸布比卡因的 4 倍，但两组血药峰浓度基本一致，可见布比卡因脂质体安全性良好[24]；另有研究将布比卡因脂质体用于 6~17 岁心脏或脊柱手术患儿，发现以 4 mg/kg 的剂量于手术切口局部注射布比卡因脂质体，血药峰浓度均在布比卡因血浆毒性阈值以下，且术后未发生严重不良事件[25]。

3 布比卡因脂质体在腹部手术患者术后镇痛中的作用

腹部手术患者术后镇痛管理效果良好，可减少疼痛中枢及外周敏化发生率，降低下肢静脉血栓发生风险，促进患者痊愈[26]。布比卡因脂质体可持续镇痛 72 h，一些国内外疾病诊疗指南推荐布比卡因脂质体应用于腹部手术术后多模式镇痛。

3.1 *腹部大手术术后镇痛* 有学者在腹腔镜肝脏切除术术后疼痛的随机对照研究中发现，术后单次注射布比卡因脂质体可显著减少术后 48 h 内阿片类药物总消耗量，同时可降低患者静息、活动疼痛评分及恶心呕吐等胃肠道反应发生风险[27]。Turan 等[28]研究按照 1∶1 将接受腹部大手术的患者分为硬膜外镇痛组、布比卡因脂质体腹横肌平面阻滞组，结果显示，布比卡因脂质体腹横肌平面阻滞组术后静息疼痛评分明显低于硬膜外镇痛组[估计差异 0.09（95%*CI*：−0.12~0.30），$P<0.05$]，但两组术后 3 d 阿片类药物消耗量无明显差异[估计差异 1.37（95%*CI*：1.05~1.79），$P=0.754$]，由此可见布比卡因脂质体在降低腹部大手术患者术后疼痛方面具有显著优势。也有研究回顾性分析全身麻醉下行下腹部大手术的成年患者临床资料发现，术后经布比卡因脂质体浸润镇痛的患者术后 0~72 h 时间加权疼痛评分明显低于术后经硬膜外自控阿片类药物镇痛的患者[29]。布比卡因脂质体主要通过腹横肌平面阻滞发挥镇痛作用，可减少阿片类药物等全身麻醉镇痛药物使用量，在应用布比卡因脂质体进行术后镇痛的前提下，观察阿片类药物使用量一定程度上可反映布比卡因脂质体镇痛效果。有研究纳入经腹横肌平面阻滞（主要药物为布比卡因脂质体）的肝切除术患者，以术后疼痛评分为主要结局，阿片类药物总消耗量为次要结局，发现与未经腹横肌平面阻滞患者相比，经腹横肌平面阻滞患者术后 24 h 疼痛评分显著降低，且口服吗啡量明显减少[30]。

3.2 *妇科手术术后镇痛* 当病情必须要进行腹部手术时，在不影响手术效果的前提下，小切口可降低对肠管的干扰，但术后仍存在较大疼痛风险。有研究证实，腹腔镜子宫切除术患者术毕在超声引导下将布比卡因脂质体用于腹横肌平面阻滞，可有效降低术后疼痛评分，减少阿片类药物使用量[31]。妇科腹腔镜手术除小切口直接诱发的疼痛外，二氧化碳气腹后导致腹膜急性扩张，形成的腹膜小血管撕裂、腹膜表面碳酸刺激等可诱发术后腹部胀痛、两侧肋部疼痛[32]。有研究在机器人辅助腹腔镜子宫切除术术前将 5 mL 布比卡因脂质体+1∶200 000 肾上腺素+5 mL 生理盐水依次注入腹横肌平面，发现相较于对照组（5 mL 盐酸布比卡因+1∶200 000 肾上腺素+5 mL 生理盐水），布比卡因脂质体组可有效降低患者术后疼痛评分，同时缩短住院时间[33]。一项随机双盲安慰剂对照试验结果显示，干预组（术后局部注射布比卡因脂质体）术后 12 h、

24 h、48 h疼痛评分(3分、3.5分、2.75分)均低于对照组(术后局部注射盐酸布比卡因)(3.5分、5分、4分),且干预组术后24~48 h追加阿片类药物率也低于对照组[34]。

3.3 胃肠手术术后镇痛 在一项关于布比卡因脂质体与标准布比卡因单独用于结直肠癌切除术的前瞻性随机对照试验中,观察组术后接受40 mL的0.125%标准布比卡因+20 mL布比卡因脂质体阻滞,对照组术后接受60 mL的0.125%标准布比卡因阻滞,结果显示,观察组术后48 h疼痛评分显著低于对照组,阿片类药物使用量少于对照组,且两组药物不良反应发生率无明显差异,可见布比卡因脂质体不仅具有良好的术后镇痛作用,且安全性良好[35]。也有研究从术后疼痛评分、肠梗阻发生率评估布比卡因脂质体在结直肠癌术后镇痛中的应用价值,发现在调整后的时间趋势分析中,应用布比卡因脂质体进行术后镇痛,可显著降低术后疼痛评分,一定程度上降低术后肠梗阻发生风险,缩短住院时间,临床可考虑将布比卡因脂质体纳入标准腹横肌平面阻滞方案[36]。有研究纳入179例接受腹腔镜Roux-en-Y胃旁路术的患者,其中89例术后注射布比卡因脂质体,90例术后注射等量布比卡因,结果显示,布比卡因脂质体组术后2~4 d服用止痛药比例明显低于布比卡因组,且术后0~72 h疼痛评分明显低于布比卡因组,说明腹腔镜Roux-en-Y胃旁路术术后注射布比卡因脂质体,镇痛效果较好[37]。也有研究采用非麻醉方式进行腹腔镜胃袖状切除术术后镇痛,以疼痛评分、术后吗啡使用量评估布比卡因脂质体术后镇痛效果,结果显示,布比卡因脂质体组术后即刻、12 h疼痛评分均低于对照组(曲马多干预),术后吗啡使用量少于对照组,镇痛效果确切[38]。

3.4 其他腹部手术术后镇痛 有研究对接受腹腔镜阑尾切除术的患者实施了腹直肌鞘阻滞与局部浸润麻醉,结果显示以布比卡因脂质体为主的腹直肌鞘阻滞的患者初始疼痛评分和术后72 h平均疼痛评分均低于以罗哌卡因为主的行局部浸润麻醉的患者,可见布比卡因脂质体在术前麻醉、术后镇痛方面均有较高应用价值[39]。一项关于腹腔镜下腹部抽脂术术后疼痛管理的研究结果显示,术后使用布比卡因脂质体镇痛的患者静脉吗啡使用频率及使用量显著低于未使用布比卡因脂质体镇痛的患者,提示布比卡因脂质体可有效缓解患者术后疼痛,降低患者不适感[40]。卢建国等[41]通过比较布比卡因脂质体与盐酸布比卡因在单孔胸腔镜肺部手术中行肋间神经阻滞后的镇痛效果发现,布比卡因脂质体组术后首次使用镇痛药物时间、术后72 h阿片类药物累计使用量均少于盐酸布比卡因组,可见布比卡因脂质体可有效降低单孔肺部手术患者术后疼痛。有研究将布比卡因脂质体用于脐疝开腹修补术,其术后120 h、10 d的加权疼痛评分均≤2.3分,低于疼痛中位评分(5.5分),且术后无其他不良事件发生,提示布比卡因脂质体镇痛效果、安全性均良好[42]。

4 小 结

布比卡因脂质体是采用脂质体技术将药物包封于类脂质双分子层内而达到长效缓释作用的新型酰胺类局部麻醉药,具有释放平稳、血药浓度稳定、镇痛时间长等特点,是腹部大手术、妇科手术、胃肠手术、腹腔镜阑尾切除术等腹部手术术后镇痛理想的局部麻醉药,为其他外科手术术后镇痛提供了新思路。但是目前,布比卡因脂质体在我国获批的适应证仅包括局部浸润镇痛、神经阻滞,使用范围有限,其有效性、安全性尚需更多高质量临床研究加以证实。

利益冲突 无

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