

瑞马唑仑稳定诱导期血流动力学但未降低腹腔镜肾部分切除术后肾损伤风险:一项倾向性评分匹配的回溯性队列研究

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摘要:目的 研究全麻诱导期使用瑞马唑仑对腹腔镜下肾部分切除术患者血流动力学及术后肾功能的影响。方法 回顾性分析2022年1月~2024年12月解放军总医院第三医学中心收治的265例接受腹腔镜下肾部分切除术(LPN)的肾肿瘤患者的临床资料。根据麻醉诱导是否使用0.2 mg/kg瑞马唑仑将患者分为对照组和瑞马唑仑组,经倾向性评分匹配后,最终纳入130例,65例/组。收集患者麻醉诱导前10 min(T_0)、诱导完成后即刻(T_1)、气管插管完成后(T_2)、气管插管后10 min(T_3)的平均动脉压(MAP)及心率(HR),收集患者术后24 h肾功能指标,并比较两组患者术后急性肾损伤(AKI)的发病率。根据术前和术后24 h血肌酐(sCr)和胱抑素(Cys-C),计算估计肾小球滤过率eGFRsCr、eGFRcys-C与eGFRdiff值。在130例患者中收集到77例术后3个月~1年的eGFRsCr,其中对照组36例,瑞马唑仑组41例,比较两组患者慢性肾脏病(CKD)的发病率以及AKI与CKD的相关性。**结果** 经倾向性评分匹配和显著协变量调整后,瑞马唑仑组 T_3 Δ MAP $[-20.11 \pm 11.65$ mmHg vs -13.54 ± 12.75 mmHg, $P < 0.05$]及 T_2 Δ HR $[-3.78 \pm 11.18$ 次/min vs 2.82 ± 10.79 次/min, $P < 0.05$]、 T_3 Δ HR $[-10.85 \pm 15.54$ 次/min vs -3.35 ± 11.67 次/min, $P < 0.05$]变化小于对照组;瑞马唑仑组术后Cys-C高于对照组 $[0.91(0.77, 1.01)$ vs $0.96(0.96, 1.03)$, $P < 0.05$];瑞马唑仑组术后24 h eGFRcys-C低于对照组 $(94.83 \pm 20.92$ vs 83.65 ± 9.84 , $P < 0.05)$;瑞马唑仑组eGFRdiff比对照组呈负向变化 $(18.55 \pm 17.06$ vs 8.52 ± 15.85 , $P < 0.05)$;其余指标差异均无统计学意义($P > 0.05$);AKI与CKD呈正相关($P < 0.05$)。**结论** 与丙泊酚相比,诱导时使用瑞马唑仑可提高麻醉诱导期血流动力学的稳定性,未降低LPN术后AKI和CKD的发病率。

关键词:瑞马唑仑;肾部分切除术;血流动力学;Cys-C;急性肾损伤;慢性肾脏病;倾向性评分匹配

Remimazolam stabilizes hemodynamics during anesthesia induction but fails to reduce renal injury risk following laparoscopic partial nephrectomy: a propensity score-matched retrospective cohort study

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Abstract: Objective To investigate the effects of remimazolam administered during anesthesia induction on hemodynamics and postoperative renal function in patients undergoing laparoscopic partial nephrectomy (LPN). **Methods** Clinical data of 265 renal tumor patients undergoing LPN between January, 2022 and December, 2024 were collected. The patients were divided into control group and remimazolam group (0.2 mg/kg for induction), and after propensity score matching (PSM), 65 patients in each group were included. Mean arterial pressure (MAP) and heart rate (HR) were recorded before induction (T_0), immediately after induction (T_1), immediately after intubation (T_2), and 10 min after intubation (T_3). Renal function indicators at 24 h postoperatively and incidences of acute kidney injury (AKI) were recorded. Estimated glomerular filtration rates (eGFRsCr, eGFRcys-C, and eGFRdiff) were calculated using serum creatinine (sCr) and cystatin C (Cys-C). From 36 patients in control group and 41 patients in remimazolam group followed up for 3-12 months, eGFRsCr data were collected to evaluate the incidence of chronic kidney disease (CKD) and analyze its correlation with AKI. **Results** After PSM and covariate adjustment, remimazolam group showed significantly smaller changes than control group in Δ MAP at T_3 (-20.11 ± 11.65 vs -13.54 ± 12.75 mmHg, $P < 0.05$), Δ HR at T_2 (-3.78 ± 11.18 vs 2.82 ± 10.79 min⁻¹, $P < 0.05$), and Δ HR at T_3 (-10.85 ± 15.54 vs -3.35 ± 11.67 min⁻¹, $P < 0.05$). The remimazolam group showed significantly higher postoperative Cys-C level than the control group $[0.96(0.96, 1.03)$ vs $0.91(0.77, 1.01)$, $P < 0.05]$ but lower eGFRcys-C at 24 h (83.65 ± 9.84 vs 94.83 ± 20.92 , $P < 0.05$). eGFRdiff showed a significant negative shift in remimazolam group (18.55 ± 17.06 vs 8.52 ± 15.85 , $P < 0.05$). Other indicators did not differ significantly between the two groups. AKI showed a significant correlation with CKD following LPN ($P < 0.05$). **Conclusion** Compared with propofol, remimazolam induction improves hemodynamic stability during anesthesia induction but does not reduce the incidences of postoperative AKI or CKD after LPN.

Keywords: remimazolam; partial nephrectomy; hemodynamics; Cystatin C; acute kidney injury; chronic kidney disease; propensity score matching

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腹腔镜下肾部分切除术(LPN)已成为肾肿瘤治疗的主要手术方式^[1],术后急性肾损伤(AKI)的发生率较高,LPN后AKI发病率高达20%~30%^[2]。发生AKI的患者慢性肾病(CKD)患病率和远期死亡率均较非AKI

患者升高,预后较差^[3]。AKI发病机制包括肾血流灌注不足、炎症和氧化应激反应、肾单位减少、缺血/再灌注损伤等^[4,5],其中围术期血流动力学波动被视为重要的危险因素。全身麻醉的诱导期是围术期血流动力学最不稳定的阶段之一,常因药物作用导致血压下降,进而影响心输出量与器官灌注^[6,7]。一项回顾性队列分析发现术中超过1/3的平均动脉压(MAP)<65 mmHg的低血压事件发生在麻醉诱导至切皮期间,这一阶段的低血压发生率是切皮后的4倍,且均与术后AKI的发生显著相关^[8]。低血压导致肾血流量减少和肾血管阻力增加,即使血压恢复后仍可能持续肾功能损害,因此在诱导期间应合理选择麻醉药物,维持血流动力学稳定以降低术后肾脏并发症的风险^[9]。

瑞马唑仑是一种新型超短效苯二氮草类麻醉药,具有起效迅速和半衰期短的特点,其通过作用于中枢神经系统 γ -氨基丁酸A受体发挥镇静作用,对心血管系统的直接抑制作用显著小于丙泊酚^[10]。已有多项随机对照试验证实,与常规诱导药物丙泊酚相比,瑞马唑仑0.2 mg/kg作为诱导药物能更有效的减少血压和心率的波动,低血压发生率更低且对升压药的需求更少^[6,9-13],能够稳定高危患者的血流动力学状态^[11]。瑞马唑仑还可以通过抑制炎症反应和氧化应激水平、抑制细胞凋亡等途径来保护重要器官功能^[14,15]。瑞马唑仑在维持血流动力学稳定方面有明确优势,且可能通过减轻血压波动维持肾脏灌注来保护肾功能,但其在LPN术中的作用尚未见研究。因此,本研究以全麻下LPN的患者为研究对象,采用倾向性评分匹配(PSM)的方法,探究麻醉诱导时使用瑞马唑仑,在LPN术中缺血-再灌注损伤的病理生理过程中是否可以通过血流动力学的稳定来实现肾功能的保护,从而为临床用药提供参考依据。

1 资料和方法

1.1 研究对象

本研究采用回顾性研究方法,选取2022年1月~2024年12月解放军总医院第三医学中心泌尿外科收治的265例全麻下接受LPN的患者临床资料。根据诱导时是否使用瑞马唑仑分为对照组($n=184$)和瑞马唑仑组($n=81$)。纳入标准:年龄>18岁;美国麻醉医师协会(ASA)I~III级;术前心、肝、肾功能正常。排除标准:术前应用肾毒性药物;肾脏二次手术病史;术前有抢救病史;术中及术后出现重大并发症。

为减少回顾性研究所带来的选择偏倚,进行PSM分析,以是否使用瑞马唑仑为因变量,以年龄、性别、体质指数(BMI)、ASA分级、高血压、糖尿病、心血管疾病、手术时间、肾动脉阻断时间、术前肌酐(sCr)、 β_2 微球蛋白(β_2 -MG)、胱抑素(Cys-C)、C反应蛋白(CRP)为自

变量,采用1:1最近邻居匹配法进行匹配,卡钳值为0.02,最终对照组和瑞马唑仑组各纳入65例。术后3月~1年共收集到其中77例患者的eGFRsCr(查阅报告及电话随访,53例患者失访且无检查报告)。本研究已获得解放军总医院第三医学中心医学伦理委员会批准(伦理批号:2025-018),并豁免知情同意。所有研究操作均符合《赫尔辛基宣言》的伦理准则。

1.2 麻醉方法

所有患者术前常规禁食禁饮。入室后,监测心电图、血氧饱和度和无创动脉血压。对照组诱导使用丙泊酚1 mg/kg,瑞马唑仑组诱导使用瑞马唑仑0.2 mg/kg,其余药物两组均采用统一诱导及维持方案:地塞米松5 mg、舒芬太尼0.3 μ g/kg、罗库溴铵0.6 mg/kg。若诱导时脑电双频指数(BIS)>60,排除干扰因素(电极片位置异常及术中医师摆放体位等)后对照组单次静推丙泊酚0.25 mg/kg,瑞马唑仑组单次静推瑞马唑仑0.05 mg/kg。气管插管后采用容量控制呼吸,调节呼吸机参数:新鲜气体流量2 L/min,潮气量6~8 mL/kg,呼吸频率12~15次/min,吸呼比1:2,吸入氧浓度60%,维持动脉血二氧化碳分压(PaCO₂)在35~45 mmHg。麻醉维持采用静-吸复合麻醉,吸入1%~1.5%七氟烷,静脉泵注丙泊酚4~12 mg/(kg·h)、瑞芬太尼5~15 μ g/(kg·h),维持BIS在40~60。在诱导给药结束即刻和气管插管完成即刻分别手动完成一次无创动脉血压测量。诱导后行桡动脉穿刺监测动脉压,必要时行中心静脉穿刺置管监测中心静脉压。术中补液首先以6~8 mL/(kg·h)输注乳酸钠林格液,根据手术情况追加舒芬太尼和罗库溴铵,并根据需要使用血管活性药物(去氧肾上腺素、去甲肾上腺素、麻黄碱、乌拉地尔等),维持动脉压在基础值的 $\pm 20\%$ 。术后镇痛采用舒芬太尼2 μ g/kg和昂丹司琼0.4 mg/kg,生理盐水配制为100 mL,以2 mL/h的速度静脉持续输注,设置Bolus剂量为0.5 mL,锁定间隔时间为15 min。

1.3 临床资料收集

收集患者临床资料,记录麻醉诱导前10 min(T_0)、诱导给药结束即刻(T_1)、气管插管完成后(T_2)、气管插管后10 min(T_3)无创动脉血压的MAP及心率(HR)。计算 T_1 、 T_2 、 T_3 时间点MAP、HR与 T_0 时间点比较的差值,分别记为 ΔMAP_1 、 ΔMAP_2 、 ΔMAP_3 、 ΔHR_1 、 ΔHR_2 、 ΔHR_3 。

根据改善全球肾脏病预后组织(KDIGO)指南诊断标准,术后48 h内sCr上升 $\geq 26.5 \mu$ mol/L或7 d内sCr上升至基线值的1.5倍,或尿量<0.5 mL/(kg·h)持续6 h及以上即诊断为AKI。AKI分为I~III期。I期:48 h内sCr上升 $\geq 26.5 \mu$ mol/L,和(或)sCr $\geq$ 基线值的1.5倍,7 d内尿量<0.5 mL/(kg·h)持续6~12 h;II期:sCr $\geq$ 基线值的2倍,尿量<0.5 mL/(kg·h)持续 ≥ 12 h;III期:sCr $\geq$ 基

线值的3倍或上升至 $\geq 353.6 \mu\text{mol/L}$ 或开始肾脏替代治疗,尿量 $<0.3 \text{ mL}/(\text{kg}\cdot\text{h})$ 持续 $\geq 24 \text{ h}$ 或无尿 $\geq 12 \text{ h}$ 。

收集患者术后3个月~1年的eGFRsCr值,以术前最近的一次的eGFRsCr为基线值,当eGFRsCr $<60 \text{ mL}/(\text{min}\cdot 1.73 \text{ m}^2)$ 时诊断为CKD。其中估算eGFRsCr通过慢性肾脏病流行病学协作组(CKD-EPI)推荐公式:

$$\text{eGFRsCr} [\text{mL}/(\text{min}\cdot 1.73 \text{ m}^2)] = 141 \times \min(\text{sCr}/\kappa, 1)^{\alpha} \times \text{Max}(\text{sCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{年龄}} \times 0.742 (\text{女性})^{[16]}$$
 κ (性别特异性常数)男性=0.9,女性=0.7; α (性别特异性指数):男性=-0.411,女性=-0.329。

$$\text{eGFRcys-C} [\text{mL}/(\text{min}\cdot 1.73 \text{ m}^2)] = 133 \times \min(\text{Cys-C}/0.839, 1)^{-0.499} \times \text{Max}(\text{Cys-C}/0.839, 1)^{-1.328} \times 0.996^{\text{年龄}} \times 0.932 (\text{女性})^{[17]}$$

$$\text{eGFRdiff} = \text{eGFRcys-C} - \text{eGFRsCr}。$$

1.4 统计学分析

本研究采用SPSS 27.0软件进行统计分析,设定双尾检验 α 水准为0.05。计量资料经正态性检验,符合正态分布者以均数 $\pm$ 标准差表示,采用两独立样本 t 检验行组间比较;非正态分布者以中位数(四分位数间距)表示,采用Mann-Whitney U 检验;计数资料以例数(百分比)表示,组间比较行 χ^2 检验或Fisher精确检验。为控制混杂偏倚,采用1:1最邻近PSM(卡钳值0.02),匹配后评估显示协变量平衡良好。对重复测量数据采用重复测量方差分析,并计算各时点与基线的差值行组间比较,对主要终点比较进行Bonferroni校正,校正后 P 值=原始 P 值 $\times 6$,以校正后 P 值 <0.05 为差异有统计学意义。考虑到回顾性研究存在的II类错误(假阴性)风险,使用G*Power 3.1.9.7进行事后效能分析。失访分析中,正态分布的连续变量采用两独立样本 t 检验,非正态分布连续变量采用Mann-Whitney U 检验,分类变量采用 χ^2 检验或Fisher精确检验。采用 χ^2 检验分析AKI与CKD的相关性。 $P<0.05$ (或校正后 $P<\alpha'$)为差异具有统计学意义。

2 结果

2.1 PSM前后两组患者围术期指标比较

匹配前,瑞马唑仑组术前 β_2 -MG、Cys-C、手术时间高于对照组($P<0.05$),其余指标差异无统计学意义($P>0.05$)。匹配后,两组各项指标差异均无统计学意义($P>0.05$,表1)。

2.2 PSM前后SMD值及组间平衡程度

PSM后,各组基线指标的标准化均差(SMD)降低(表2),PSM有效改善了组间基线特征的平衡性,降低了混杂因素干扰。

2.3 PSM后两组患者不同时间点MAP及HR变化情况比较

重复测量方差分析显示,两组患者 ΔMAP 与 ΔHR

的变化模式存在整体差异。其中, ΔMAP 存在显著的“时间 $\times$ 组别”交互效应($P=0.038$)。经Bonferroni校正的组间比较显示,瑞马唑仑组在T3时间点的血压降幅(ΔMAP_3)以及在T2、T3时间点的心率波动(ΔHR_2 、 ΔHR_3)均小于对照组(校正后 $P<0.05$)。其余时间点差异无统计学意义(表3)。

2.4 PSM后两组患者围术期指标比较

瑞马唑仑组术后24 h Cys-C高于对照组,eGFRcys-C低于对照组,eGFRdiff呈负向变化($P<0.05$)。两组患者术后AKI发病率差异无统计学意义($P=0.56$),事后效能分析显示,该阴性结果的统计效能为0.06,存在较高的假阴性风险。其余指标差异均无统计学意义($P>0.05$,表4)。

2.5 PSM后两组患者各年龄段AKI的发病率比较

将两组患者按年龄分组后显示,各年龄段的AKI发病率差异均无统计学意义($P>0.05$,表5)。

2.6 随访患者与失访患者围术期指标比较

77例随访患者与53例失访患者的性别、手术时间、术前sCr、术前Cys-C、术前eGFRsCr的差异具有统计学意义($P<0.05$),其余指标差异无统计学意义($P>0.05$,表6)。

2.7 患者围术期指标以及术后AKI和CKD比较

本研究共收集到77例患者术后3个月~1年的sCr和Cys-C,其中对照组36例,瑞马唑仑组41例。两组术后Cys-C中位数相近,但Mann-Whitney U 检验显示其整体分布差异存在统计学意义($P=0.008$)。瑞马唑仑组肾动脉阻断时间长于对照组($P<0.05$),术后eGFRcys-C低于对照组($P<0.05$),术后eGFRdiff比对照组呈负向变化($P<0.05$),其余结果差异无统计学意义($P>0.05$)。两组患者术后AKI和CKD的发病率差异均无统计学意义($P>0.05$,表7)。事后效能分析显示,该阴性结果的统计效能为0.17,存在较高的假阴性风险。

2.8 随访患者不同时间点MAP及HR变化情况比较

重复测量方差分析显示,两组患者 ΔMAP 与 ΔHR 的变化模式不存在显著的整体差异。其中, ΔMAP 的“时间 $\times$ 组别”交互效应($P=0.379$)与 ΔHR 的“时间 $\times$ 组别”交互效应($P=0.702$)均无统计学意义,两组血压、心率随时间的变化轨迹相似。经Bonferroni校正的组间比较显示,两组在各时间点的血压降幅及心率波动差异均无统计学意义(校正后 $P>0.05$,表8)。

2.9 术后AKI与CKD的相关性

77例患者中,31例发生AKI,25例发生CKD。相关分析显示,术后AKI与CKD呈正相关($P<0.01$,表9)。

3 讨论

AKI是LPN术后常见的并发症,且与患者CKD患病率及远期死亡率升高密切相关,本研究发现,麻醉诱

表1 两组患者PSM前后基线特征比较

Tab.1 Comparison of baseline characteristics between the two groups before and after propensity score matching (PSM)

Variable	Before PSM				After PSM			
	Control group (n=184)	Remimazolam group (n=81)	$t/\chi^2/z$	P	Control group (n=65)	Remimazolam group (n=65)	$t/\chi^2/z$	P
Age (year, <i>Mean</i> ± <i>SD</i>)	52±14	54±12	-1.148	0.252	53±15	54±11	-0.448	0.655
Male/Female (n)	122/62	53/28	0.019	0.890	46/19	46/19	0.000	1.000
BMI (kg/m ² , <i>Mean</i> ± <i>SD</i>)	25.42±12.37	25.58±11.47	-0.348	0.728	25.61±4.15	25.83±3.22	-0.335	0.738
ASA [n (%)]			1.208	0.751			1.592	0.661
I	40 (21.7)	14 (17.3)			11 (16.9)	12 (18.5)		
II	133 (72.3)	63 (77.8)			48 (73.8)	49 (75.4)		
III	11 (6.0)	4 (4.9)			6 (9.2)	4 (6.2)		
Combined disease [n (%)]								
Diabetes	25 (13.6)	12 (14.8)	0.071	0.79	9 (13.8)	11 (16.9)	0.236	0.627
Hypertension	70 (38.0)	25 (30.9)	1.260	0.262	25 (38.5)	24 (36.9)	0.033	0.856
Cardiovascular disease	23 (12.5)	12 (14.8)	0.263	0.608	11 (16.9)	12 (18.5)	0.053	0.818
Operation time [min, M (P ₂₅ , P ₇₅)]	126.50 (105.50, 148.00)	130.00 (110.00, 170.00)	1.975	0.048	135.0 (110.0, 157.5)	130.0 (110.0, 162.50)	-0.021	0.983
Renal artery occlusion time [min, M (P ₂₅ , P ₇₅)]	23.00 (16.25, 28.00)	21.00 (17.00, 27.00)	-0.602	0.547	22.0 (15.0, 28.0)	23.0 (17.50, 27.0)	0.545	0.585
Preoperative sCr [μmol/L, M (P ₂₅ , P ₇₅)]	67.0 (56.0, 77.0)	68.0 (55.0, 77.5)	-0.064	0.949	69.00 (60.50, 76.50)	69.00 (55.50, 76.50)	-0.431	0.667
Preoperative β ₂ -MG [mg/L, M (P ₂₅ , P ₇₅)]	1.61 (1.38, 1.92)	2.03 (1.85, 2.29)	6.896	<0.01	2.03 (1.69, 2.37)	2.01 (1.86, 2.23)	0.123	0.902
Preoperative Cys-C [mg/L, M (P ₂₅ , P ₇₅)]	0.77 (0.68, 0.88)	0.84 (0.84, 0.90)	4.926	<0.01	0.84 (0.80, 0.97)	0.84 (0.84, 0.90)	-0.060	0.956
Preoperative CRP [mg/L, M (P ₂₅ , P ₇₅)]	1.49 (0.66, 4.56)	1.50 (0.72, 5.80)	0.474	0.635	1.48 (0.52, 5.93)	1.62 (0.69, 5.30)	-0.228	0.820
Preoperative eGFRsCr [mL/(min·1.73 m ²), <i>Mean</i> ± <i>SD</i>]	91.47±16.60	91.00±16.44	0.216	0.829	89.69±18.48	91.59±16.76	-0.614	0.540
Preoperative eGFRcys-C [mL/(min·1.73 m ²), M (P ₂₅ , P ₇₅)]	109.25 (96.58, 119.25)	103.16 (90.79, 109.56)	-3.957	<0.01	101.93 (82.65, 112.99)	103.99 (91.63, 108.24)	0.102	0.918
Preoperative eGFRdiff [mL/(min·1.73 m ²), <i>Mean</i> ± <i>SD</i>]	14.51±16.98	7.59±16.62	3.075	0.002	6.94±15.46	7.81±13.71	-0.339	0.735

BMI:Body mass index; ASA: American Society of Anesthesiologists physical status classification; Preoperative sCr: Preoperative serum creatinine; Preoperative β₂-MG:Preoperative β₂-Microglobulin; Preoperative Cys-C: Preoperative Cystatin-C; Preoperative CRP: Preoperative C-reactive protein; Preoperative eGFRsCr: Preoperative estimated glomerular filtration rate based on serum creatinine; Preoperative eGFRcys-C: Preoperative estimated glomerular filtration rate based on Cystatin-C; Preoperative eGFRdiff: Preoperative eGFRcys-C-Preoperative eGFRsCr.

表2 PSM前后SMD值及组间平衡程度

Tab.2 SMD and intergroup balance status before and after PSM

Variable	SMD before PSM	SMD after PSM	Balance status (After PSM)
Age	0.144	0.079	Good (<0.1)
Male/Female	0.018	0	Good (<0.1)
BMI	0.046	0.059	Good (<0.1)
ASA	0.07	0.093	Good (<0.1)
Combined disease			
Diabetes	0.035	0.085	Good (<0.1)
Hypertension	0.15	0.032	Good (<0.1)
Cardiovascular disease	0.068	0.04	Good (<0.1)
Operation time	0.363	0.03	Good (<0.1)
Renal artery occlusion time	0.084	0.014	Good (<0.1)
Preoperative sCr	0.062	0.187	Acceptable (0.1~0.2)
Preoperative β ₂ -MG	0.817	0.082	Good (<0.1)
Preoperative Cys-C	0.458	0.202	Acceptable (0.1~0.2)
Preoperative CRP	0.098	0.114	Acceptable (0.1~0.2)

表3 PSM后两组不同时间点MAP及HR变化情况比较
Tab.3 Comparison of changes in MAP and HR among the two groups at different time points ($n=65$, $Mean\pm SD$)

Group	ΔMAP (mmHg)			ΔHR (beat/min)		
	ΔMAP_1	ΔMAP_2	ΔMAP_3	ΔHR_1	ΔHR_2	ΔHR_3
Control	-4.62 $\pm$ 8.75	-9.38 $\pm$ 12.97	-20.11 $\pm$ 11.65	-2.09 $\pm$ 9.50	-3.78 $\pm$ 11.18	-10.85 $\pm$ 15.54
Remimazolam	-2.71 $\pm$ 6.72	-7.15 $\pm$ 12.07	-13.54 $\pm$ 12.75	0.63 $\pm$ 6.00	2.82 $\pm$ 10.79	-3.35 $\pm$ 11.67
t	-1.395	-1.015	-3.067	-1.954	-3.426	-3.108
P	0.165	0.312	0.003	0.053	0.001	0.002
Corrected P -value	0.990	1.000	0.018	0.318	0.006	0.012

MAP: Mean arterial pressure; HR: Heart rate.

表4 PSM后两组患者围术期指标比较
Tab.4 Comparison of perioperative characteristics between the two groups after PSM ($n=65$)

Variable	Control group	Remimazolam group	P
Renal artery occlusion time [min, M (P_{25} , P_{75})]	22.0 (15.0, 28.0)	23.0 (17.5, 27.0)	0.585
Operation time [min, M (P_{25} , P_{75})]	135 (110, 158)	130 (110, 163)	0.983
Blood loss [mL, M (P_{25} , P_{75})]	100 (50, 100)	100 (100, 100)	0.565
Urine output [mL, M (P_{25} , P_{75})]	100 (100, 250)	100 (100, 200)	0.082
Crystalloid fluid intake [mL, M (P_{25} , P_{75})]	1500 (1000, 1500)	1000 (1000, 1500)	0.065
Colloid fluid intake [mL, M (P_{25} , P_{75})]	0 (0, 500)	0 (0, 500)	0.482
Postoperative sCr [μ mol/L, M (P_{25} , P_{75})]	85.0 (70.0, 101.5)	84.0 (70.5, 103.5)	0.927
Postoperative β_2 -MG [mg/L, M (P_{25} , P_{75})]	1.94 (1.62, 2.25)	2.07 (2.03, 2.17)	0.467
Postoperative Cys-C [mg/L, M (P_{25} , P_{75})]	0.91 (0.77, 1.01)	0.96 (0.96, 1.03)	0.001
postoperative eGFRsCr [mL/(min $\cdot$ 1.73 m ^{2}), $Mean\pm SD$]	76.29 $\pm$ 19.49	75.13 $\pm$ 18.96	0.734
postoperative eGFRcys-C [mL/(min $\cdot$ 1.73 m ^{2}), $Mean\pm SD$]	94.83 $\pm$ 20.92	83.65 $\pm$ 9.84	<0.01
postoperative eGFRdiff [mL/(min $\cdot$ 1.73 m ^{2}), $Mean\pm SD$]	18.55 $\pm$ 17.06	8.52 $\pm$ 15.85	0.001
Postoperative CRP [mg/L, M (P_{25} , P_{75})]	27.40 (13.03, 41.44)	31.58 (16.97, 51.70)	0.397
Postoperative AKI [n (%)]	17 (26.2)	20 (30.8)	0.560

Postoperative sCr: Postoperative serum creatinine; Postoperative β_2 -MG: Postoperative β_2 -Microglobulin; Postoperative Cys-C: Postoperative Cystatin-C; Postoperative eGFRsCr: Postoperative estimated glomerular filtration rate based on serum creatinine; Postoperative eGFRcys-C: Postoperative estimated glomerular filtration rate based on Cystatin-C; Postoperative eGFRdiff: Postoperative eGFRcys-C-Postoperative eGFRsCr; Postoperative CRP: Postoperative C-reactive protein; Postoperative AKI: Postoperative acute kidney injury.

表5 PSM后两组患者各年龄段AKI发病率的比较
Tab.5 Comparison of AKI incidence among different age groups between the two groups after PSM ($n=65$)

Age (year)	Control group		Remimazolam group($n=65$)		P
	n	AKI [n (%)]	n	AKI [n (%)]	
18-44	21	3 (14.29)	14	3 (21.43)	0.583
45-64	25	6 (24.00)	39	14 (35.90)	0.316
≥ 65	19	8 (42.11)	12	3 (25.00)	0.332

AKI: Acute kidney injury.

导期给予0.2 mg/kg的瑞马唑仑可提升麻醉诱导期血流动力学稳定性,但这一优势并不能降低LPN术后AKI和CKD的发病率。全身血流动力学稳定是肾脏灌注稳定的前提。研究发现在高动力感染性休克动物模型中随着心输出量的升高,肾血流量可升高达2倍以上^[18]。由此证明,全身血流动力学状态对肾脏的灌注影响很

大。若术中肾脏组织出现低灌注,术后发生AKI风险会大大增加^[19, 20]。因此,维持围术期血流动力学状态稳定对预防术后AKI至关重要。在妇科、肝癌、髋关节等手术中,诱导期使用瑞马唑仑,围术期不良反应发生率,可减轻气管插管等应激反应,有效提升患者围术期血流动力学的稳定性^[21]。与本研究全身麻醉诱导期使用

表6 随访患者与失访患者围术期指标比较

Tab.6 Comparison of perioperative indicators between followed-up patients and patients lost to follow-up

Variable	Follow-up group group (n=77)	Lost to follow-up group group (n=53)	<i>t</i> / <i>χ</i> ² / <i>z</i>	<i>P</i>
Age (year, <i>Mean</i> ± <i>SD</i>)	55±13	52±13	-1.192	0.235
Male/Female (<i>n</i>)	60/17	32/21	4.671	0.031
BMI (kg/m ² , <i>Mean</i> ± <i>SD</i>)	25.99±3.51	25.33±3.97	-1.001	0.319
ASA [<i>n</i> (%)]			4.216	0.239
I	11 (14.28)	12 (22.64)		
II	58 (75.32)	39 (73.58)		
III	8 (10.39)	2 (3.8)		
Combined disease [<i>n</i> (%)]				
Diabetes	10 (12.99)	10	0.834	0.361
Hypertension	33 (42.86)	16 (30.19)	2.145	0.143
Cardiovascular disease	16 (20.78)	7 (13.21)	1.236	0.266
Operation time [min, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	125 (105, 155)	140 (120, 175)	-2.777	0.005
Renal artery occlusion time [min, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	22.0 (15.5, 27.0)	23.0 (17.0, 29.5)	-0.837	0.402
Preoperative sCr [μmol/L, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	72.0 (65.0, 78.5)	66.0 (54.0, 71.0)	3.477	0.001
Preoperative β ₂ -MG [mg/L, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	2.04 (1.78, 2.38)	2.01 (1.70, 2.20)	1.144	0.253
Preoperative Cys-C [mg/L, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	0.84 (0.84, 1.02)	0.84 (0.82, 0.89)	2.037	0.042
Preoperative CRP [mg/L, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	1.48 (0.58, 5.36)	1.62 (0.61, 6.04)	-0.190	0.850
Preoperative eGFRsCr [mL/(min·1.73 m ²), <i>Mean</i> ± <i>SD</i>]	95.50±16.90	102.69±10.51	2.984	0.003

BMI: Body mass index; ASA: American Society of Anesthesiologists physical status classification; Preoperative sCr: Preoperative serum creatinine; Preoperative β₂-MG: Preoperative β₂-Microglobulin; Preoperative Cys-C: Preoperative Cystatin-C; Preoperative CRP: Preoperative C-reactive protein; Preoperative eGFRsCr: Preoperative estimated glomerular filtration rate based on serum creatinine.

瑞马唑仑 MAP 和 HR 整体波动幅度均呈减小趋势的结果一致,说明全身麻醉诱导期使用 0.2 mg/kg 瑞马唑仑后可使患者血流动力学更加稳定。平稳的血流动力学有助于维持肾脏灌注,对肾功能具有一定的保护作用^[22]。有研究在肝切除术患者中发现^[23],在瑞马唑仑全身麻醉下采用中心静脉压指导的液体管理,可显著降低术后 AKI 发生率及术后 24 h、48 h sCr 水平,提示瑞马唑仑复合优化的围术期管理策略可能对肾功能产生保护作用。

在 LPN 手术过程中,肾动脉阻断/开放会引起肾脏缺血和再灌注损伤^[24],肾动脉阻断时间是影响 LPN 术后肾功能的关键独立危险因素^[25]。在本研究随访的 77 例患者中,两组诱导期血流动力学的变化差异无统计学意义,这可能与失访率高,随访样本可能存在选择性偏倚相关。瑞马唑仑组的肾动脉阻断时间长于对照组,而 AKI 和 CKD 发病率无显著区别,这说明在 77 例患者中,虽然瑞马唑仑未改善诱导期血流动力学,但单次给药对患者的肾功能仍可能存在保护作用。后期需通过提高远期随访率、手术过程中持续给药^[26]等措施,采用前瞻性随机对照的方法进一步研究。

Cys-C 是一种低相对分子质量的碱性非糖基化蛋白质,其在血液中的水平不受肌肉量、营养状态及肝功能等因素的影响,是更敏感的肾小球滤过标志物,其早

期升高常提示更细微的肾功能变化^[17, 27]。在轻度肾损伤后 Cys-C 会在 sCr 升高前 1~2 d 开始升高,并随着病情进展逐渐升高^[28]。一项新生儿研究表明,Cys-C 是检测新生儿肾功能的可靠且敏感的生物标志物^[29]。本研究中,瑞马唑仑组术后 Cys-C 水平在统计学意义上高于对照组,但其中位数差异极小(0.005 mg/L),其临床意义尚不明确,可能与较大的样本量使得微小的差异也能被检出有关,后续需前瞻性研究作验证。瑞马唑仑的代谢虽不依赖肝肾功能,但其主要的代谢产物 CNS 7054 仍需经肾脏排泄^[30],但该代谢产物对 Cys-C 的作用目前尚无研究。术后 Cys-C 短暂升高的原因不能排除瑞马唑仑或其代谢产物对 Cys-C 的肾小管重吸收或代谢清除产生短暂的、药理学意义上的影响,瑞马唑仑对肾功能的影响作用尚存在疑问,但血流动力学稳定仍然是瑞马唑仑的客观优势。

随着 Cys-C 在临床中的应用越来越普遍,人们也意识到:许多患者的 eGFR Cys-C 与 eGFRsCr 之间存在差异^[31]。因此,我们使用慢性肾脏病流行病学合作组织(CKD-EPI)推荐的计算公式^[16, 17],分别计算 eGFR Cys-C、eGFRsCr 及差值 eGFRdiff(eGFR Cys-C-eGFRsCr)。此前有研究表明 eGFRdiff 差值越负,与多种不良结局风险增加相关,包括药物相关不良事件、急性肾损伤、心

表7 77例患者围术期指标及术后AKI和CKD比较
Tab.7 Comparison of perioperative characteristics and postoperative AKI and CKD among 77 patients

Variable	Control group (<i>n</i> =36)	Remimazolam group (<i>n</i> =41)	<i>P</i>
Age (year, <i>Mean</i> ± <i>SD</i>)	55±16	55±11	0.767
Male/Female (<i>n</i>)	28/8	32/9	0.977
BMI (kg/m ² , <i>Mean</i> ± <i>SD</i>)	25.49±3.93	26.43±3.07	0.241
Operation time [min, M (P ₂₅ , P ₇₅)]	123 (105, 145)	125 (105, 158)	0.556
Renal artery occlusion time [min, M (P ₂₅ , P ₇₅)]	19 (15, 25)	25 (20, 28)	0.035
Crystalloid fluid intake [mL, M (P ₂₅ , P ₇₅)]	1500 (1000, 1500)	1000 (1000, 1500)	0.083
Colloid fluid intake [mL, M (P ₂₅ , P ₇₅)]	0 (0, 500)	0 (0, 500)	0.193
Preoperative sCr [μmol/L, M (P ₂₅ , P ₇₅)]	72.00 (64.25, 83.50)	72.00 (65.50, 78.00)	0.728
Preoperative β2-MG [mg/L, M (P ₂₅ , P ₇₅)]	2.05 (1.70, 2.50)	2.04 (1.87, 2.35)	0.955
Preoperative Cys-C [mg/L, M (P ₂₅ , P ₇₅)]	0.85 (0.79, 1.07)	0.84 (0.84, 0.95)	0.627
Preoperative eGFRsCr [mL/(min·1.73 m ²), M (P ₂₅ , P ₇₅)]	89.59 (76.40, 101.61)	95.85 (78.20, 107.50)	0.300
Preoperative eGFRcys-C [mL/(min·1.73 m ²), M (P ₂₅ , P ₇₅)]	100.7 (71.50, 114.30)	103.16 (88.22, 107.81)	0.818
Preoperative eGFRdiff [mL/(min·1.73 m ²), M (P ₂₅ , P ₇₅)]	4.77 (-5.60, 16.60)	2.85 (-4.69, 12.39)	0.642
Preoperative CRP [mg/L, M (P ₂₅ , P ₇₅)]	1.53 (0.49, 4.66)	1.31 (0.69, 6.04)	0.890
Postoperative sCr [μmol/L, M (P ₂₅ , P ₇₅)]	96.50 (72.75, 113.25)	90.00 (81.50, 116.50)	0.732
Postoperative β2-MG [mg/L, M (P ₂₅ , P ₇₅)]	2.07 (1.52, 2.55)	2.07 (2.07, 2.33)	0.148
Postoperative Cys-C [mg/L, M (P ₂₅ , P ₇₅)]	0.955 (0.763, 1.068)	0.960 (0.960, 1.065)	0.008
Postoperative eGFRsCr[mL/ (min·1.73 m ²), M (P ₂₅ , P ₇₅)] (3 months to 1 year postoperatively)	81.40 (54.93, 106.13)	84.20 (59.25, 100.00)	0.992
Postoperative eGFRsCr[mL/ (min·1.73 m ²), M (P ₂₅ , P ₇₅)] (24 hours postoperatively)	71.75 (56.70, 81.29)	72.29 (53.73, 86.02)	0.951
Postoperative eGFRcys-C [mL/(min·1.73 m ²), M (P ₂₅ , P ₇₅)] (24 hours postoperatively)	94.84 (72.70, 112.27)	83.81 (75.51, 89.29)	0.013
Postoperative eGFRdiff [mL/(min·1.73 m ²), M (P ₂₅ , P ₇₅)] (24 hours postoperatively)	20.61 (10.30, 34.96)	6.95 (-3.80, 21.55)	0.020
Postoperative CRP [mg/L, M (P ₂₅ , P ₇₅)]	25.05 (14.24, 39.34)	30.89 (15.77, 52.58)	0.491
Postoperative AKI [<i>n</i> (%)]	14 (38.89)	17 (41.46)	0.818
CKD [<i>n</i> (%)]	14 (38.89)	11 (26.83)	0.259

AKI: Postoperative acute kidney injury; CKD: Chronic kidney disease.

表8 PSM后两组不同时间点MAP及HR变化情况比较
Tab.8 Comparison of changes in mean arterial pressure (MAP) and heart rate (HR) among the two groups at different time points (*Mean*±*SD*)

Group	ΔMAP (mmHg)			ΔHR (beat/min)		
	ΔMAP ₁	ΔMAP ₂	ΔMAP ₃	ΔHR ₁	ΔHR ₂	ΔHR ₃
Control group (<i>n</i> =36)	-5.11±7.82	-11.64±12.33	-20.56±12.00	-2.75±7.17	-2.81±11.76	-10.28±16.45
Remimazolam group (<i>n</i> =41)	-3.37±7.19	-8.49±13.29	-15.12±13.74	0.78±6.98	2.61±11.01	-4.24±11.36
<i>t</i>	-1.020	-1.073	-1.836	-2.187	-2.086	-1.892
<i>P</i>	0.340	0.163	0.453	0.785	0.815	0.061
Corrected <i>P</i> -value	1.000	0.978	1.000	1.000	1.000	0.366

MAP:Mean arterial pressure;HR:Heart rate .

表9 患者术后AKI与CKD的关联性
Tab.9 Correlation between AKI and CKD in 77 patients[*n* (%)]

Postoperative AKI	CKD		χ^2	<i>r</i>	<i>P</i>
	No	Yes			
No	39 (75.0)	7 (28.0)	15.506	0.449	<0.01
Yes	13 (25.0)	18 (72.0)			

血管疾病、肾衰竭及全因死亡率^[32, 33]。本研究发现,瑞马唑仑组患者术后24 h的eGFRdiff呈负向变化,即eGFRcys-C较eGFRsCr的下降更为明显。这种eGFR的差异可能源于Cys-C和sCr两种标志物反映肾小球滤过功能的不同方面,Cys-C对早期滤过功能下降可能更为敏感^[34],结合瑞马唑仑组术后Cys-C短暂升高这一现

象,进一步说明瑞马唑仑可能对术后近期的肾功能产生不利影响,代表了一种亚临床的、可逆的肾小球功能波动。研究表明,将eGFRdiff值纳入CKD风险评估可以提高对肾功能下降高风险患者的识别能力,eGFRdiff差值越负,发展为CKD以及eGFR快速下降的风险会更高^[35]。本研究中,两组患者术后AKI和CKD的发生率无差异,可能是由于二者均是以术后sCr为指标进行诊断所导致,也可能是因为样本量不足导致的假阴性。因此术后短暂Cys-C升高及eGFRdiff的负向变化对患者近期和远期肾功能是否具有相关性,仍需扩大样本量进行研究验证。目前尚无直接文献解释瑞马唑仑影响Cys-C水平的分子及生理机制。

本研究对远期CKD的发病率存在较高的失访率(40.8%)。失访分析显示,两组在性别、手术时间、术前sCr、术前Cys-C及术前eGFRsCr存在差异($P<0.05$),且随访组患者术前肾功能基线水平较失访组更差,且手术时间更短,提示随访样本可能存在选择性偏倚,肾功能基础较差的患者更倾向于完成随访。本研究中两组术后AKI与CKD的关联性仍有统计学意义,与既往研究中结论一致^[36-39]。但本研究由于失访率较高,且失访组与随访组在多个关键指标上存在显著差异,可能存在选择性偏倚,因此AKI发病率与CKD发病率关联性结果需要谨慎地解读。本研究的局限性:缺少术后长期的动态数据,无法对肾功能演变进行深入分析。样本量小导致统计效能不足,关于AKI和CKD发病率无显著差异的阴性结论应谨慎解读,仅作为探索性假设。后期需多中心、随机对照研究进一步探究瑞马唑仑对于肾脏的影响。

综上,在LPN术中麻醉诱导时使用0.2 mg/kg瑞马唑仑能更有效的稳定麻醉诱导期的血流动力学,但这一优势并未降低患者术后AKI及CKD的发病率。

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