

· 临床研究 ·

曲美他嗪预防肾功能不全患者造影剂肾病的 Meta 分析

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【摘要】目的 系统评价曲美他嗪(TMZ)预防肾功能不全患者造影剂肾病(CIN)的临床疗效。**方法** 计算机检索PubMed、Embase、Cochrane Library、EBSCO与Scopus数据库,检索时间为建库至2018年12月,同时查阅相关会议摘要和网站。采用RevMan 5.3软件进行Meta分析。**结果** 最终纳入符合要求的文献6篇,共920例患者。其中,TMZ(+)组456例,TMZ(-)组464例。荟萃分析结果显示,TMZ(+)组的CIN发生率明显低于TMZ(-)组($OR=0.31$, $95\%CI 0.20\sim0.48$; $P<0.01$);术后3d内患者的血清肌酐值在TMZ(+)组更低,但与TMZ(-)组相比,尚未达到统计学差异($MD=-0.22$, $95\%CI -0.48\sim0.04$; $P=0.10$)。**结论** TMZ对预防肾功能不全患者CIN的发生具有积极作用。不过,TMZ对血清肌酐水平的真实影响,仍需要更多高质量、大样本的随机对照研究进一步证实。

【关键词】 曲美他嗪;造影剂肾病;肾功能不全;Meta分析

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Trimetazidine for prevention of contrast-induced nephropathy in patients with renal insufficiency: a Meta-analysis

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【Abstract】 Objective To systematically evaluate the efficacy of trimetazidine (TMZ) in the prevention of contrast-induced nephropathy (CIN) in patients with renal insufficiency. **Methods** The databases, including PubMed, Embase, Cochrane Library, EBSCO and Scopus from inception to December 2018 were searched for eligible trials evaluating the clinical efficacy of TMZ in the prevention of CIN. Meanwhile, we reviewed the relevant conference summary and websites. Meta-analysis was performed using RevMan 5.3 statistics. **Results** A total of 6 studies, involving 920 patients, with 456 patients in TMZ (+) group and 464 patients in TMZ (-) group were collected. Meta-analysis showed that the incidence of CIN in TMZ (+) group was significantly lower than TMZ (-) group ($OR=0.31$, $95\%CI 0.20-0.48$; $P<0.01$). The serum creatinine (SCr) level was lower in TMZ (+) group than the other group within 3 d after procedure, but there was no statistical difference ($MD=-0.22$, $95\%CI -0.48-0.04$; $P=0.10$). **Conclusion** TMZ shows a positive effect on the prevention of CIN in patients with renal insufficiency. However, more high-quality, large-sample randomized controlled trials are still needed to further confirm its efficacy.

【Key words】 trimetazidine; contrast-induced nephropathy; renal insufficiency; Meta-analysis

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冠状动脉造影过程中,造影剂肾病(contrast-induced nephropathy, CIN)是导致患者发生急性肾功能衰竭的重要原因^[1]。肾功能不全患者CIN的发病率更高,已成为介入医师应用造影剂的首要顾虑。CIN定义为术后患者血清肌酐(serum creatinine, SCr)绝对值升高超过0.5 mg/dl,或术后24~72 h内SCr较基线值增加25%以上^[2]。近年来,研究者报

道了多种预防CIN的方法,然而这些研究的结论仍存在一定争议。曲美他嗪(trimetazidine, TMZ)是一种抗细胞缺血剂,多项研究^[3-5]发现TMZ是预防肾功能不全患者CIN极具潜力的药物。不过,由于各研究样本量相对较小,统计学把握度可能不足,因此,我们综合了已有研究进行本次荟萃分析,以明确TMZ预防肾功能不全患者CIN的临床效果,从而为

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临床治疗提供理论依据。

1 对象与方法

1.1 纳入和排除标准

纳入标准:(1)在同行评审英文期刊上发表的随机对照研究;(2)研究对象为接受冠状动脉造影的肾功能不全患者,研究目的是评估TMZ应用与否对预防CIN的疗效;(3)至少包括以下一项结局指标,即CIN发生率及造影前后SCr变化。

排除标准:(1)混杂其他干预措施,无法比较TMZ应用与否对临床结局的影响;(2)无法提取临床数据的文献;(3)纳入相同人群重复发表的文献。临床终点包括:(1)CIN发生率;(2)术后3 d内的SCr值。

1.2 文献检索策略

计算机检索PubMed、Embase、Cochrane Library、EBSCO与Scopus数据库。检索时间设定为建库至2018年12月。英文检索词包括:trimetazidine、TMZ、contrast-induced nephropathy、renal insufficiency、coronary angiography、percutaneous coronary intervention、PCI。同时查阅相关会议摘要和网站,并回顾参考文献和早期发表的Meta分析,纳入所有符合标准的随机对照研究。

1.3 文章筛选及质量评价

由2名研究员按照检索策略独立完成检索,当有分歧时,与第3名研究员讨论决定。根据改良的Jadad量表(随机序列的产生、随机化隐藏、盲法和失访评估),评价研究质量(1~3分为低质量,4~7分为高质量)。提取包括研究设计情况、研究对象临床基线特征、临床终点等资料。

1.4 统计学处理

采用RevMan 5.3软件进行Meta分析。通过固定或随机效应模型计算比值比(odds ratio, OR)和95%置信区间(95% confidence interval, 95% CI),设定显著性水平为0.05。采用卡方检验分析统计学异质性($I^2 > 50%$, $P < 0.1$ 表示有统计学异质性),敏感性分析检验合并结果的稳健性,Egger回归图检测发表偏倚。

2 结果

2.1 文献检索结果

初检文献564篇,进一步阅读筛选后,最终纳入符合要求的文献6篇^[3, 6-10]。具体筛选流程和结果见图1。

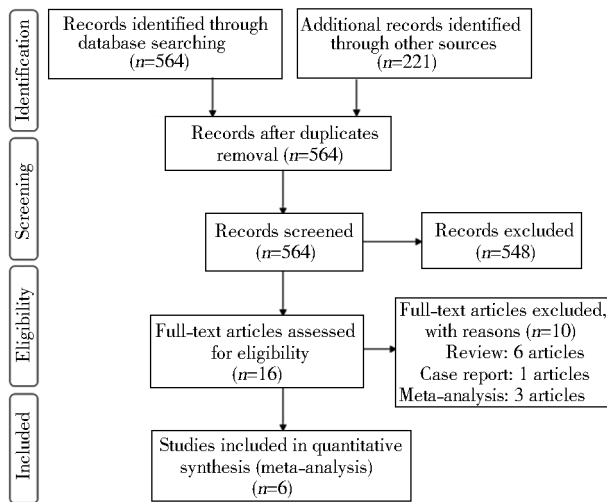


图1 文献筛选流程图

Figure 1 Literature screening flow chart

2.2 文献质量评价及患者基线特征

最终纳入的6篇文献,Jadad评分均 ≥ 4 分,共包括920例患者,曲美他嗪组[TMZ(+)]共456例,对照组[TMZ(-)]共464例。所有患者均合并有轻-中度肾功能不全。有5篇文献^[3, 6, 8-10]研究的是单纯水化对比水化联合TMZ的疗效,有1篇文献^[7]研究的是水化+N-乙酰半胱氨酸联合TMZ对比水化+N-乙酰半胱氨酸的疗效。6篇文献中有2篇^[3, 7]使用的造影剂是碘普罗胺,2篇文献^[8, 10]中造影剂为碘克沙醇,其余2篇文献^[6, 9]均只列述了造影剂的性质(非离子低渗/等渗型);2组患者基线特征(年龄、性别、糖尿病、高血压等)比较,差异无统计学意义($P > 0.05$;表1)。

2.3 CIN发生率

纳入的6篇文献均比较了TMZ(+)组和TMZ(-)组的CIN发生率。TMZ(+)组有30例患者发生CIN,而TMZ(-)组有85例患者发生CIN。Meta分析结果显示:TMZ(+)组的CIN发生率明显低于TMZ(-)组($OR = 0.31$, $95\% CI 0.20 \sim 0.48$; $P < 0.01$;图2)。

2.4 基线水平及术后3 d内SCr值变化

纳入的6篇文献中,有4篇报道了术后SCr水平。Onbasili等^[3]记录了基线、术后2 d及7 d的SCr水平;Shehata等^[7]记录了基线、术后3 d及10 d的SCr水平;Ibrahim等^[9]记录了基线、术后1 d及3 d的SCr水平;Liu等^[8]记录了基线、术后1 d、2 d及3 d的SCr水平。对术前及术后SCr值进行Meta分析,结果显示:TMZ(+)组及TMZ(-)组SCr值在基线水平无统计学差异($MD = 0.03$, $95\% CI -0.02 \sim 0.08$;

$P=0.26$), 见图 3。术后 3 d 内的 SCr 水平 (Onbasili 等^[3]的研究中以第 2 天 SCr 值表示 3 d 内 SCr 水平) 在 TMZ (+) 组更低, 但同 TMZ (-) 组相比, 尚未达到统计学差异 ($MD = -0.22, 95\% CI -0.48 \sim 0.04; P=0.10$), 见图 4。

2.5 敏感性分析和发表偏倚评价

除术后 3 d 内 SCr 值比较存在异质性 ($I^2 = 89\%$), 采用随机效应模型外, CIN 发生率及基线 SCr 值比较不存在异质性, 故采用固定效应模型。敏感性分析中, 剔除任一研究均未改变总体统计学结果。通

表 1 纳入文献的基本情况

Table 1 Baseline information of enrolled studies

Study	Sample size		Age (years)		Male (%)		DM (%)		HT (%)		Contrast-medium	Jadad score
	TMZ (+)	TMZ (-)	TMZ (+)	TMZ (-)	TMZ (+)	TMZ (-)	TMZ (+)	TMZ (-)	TMZ (+)	TMZ (-)		
	Onbasili 2007 ^[3]	40	42	61.0±10.0	60.0±11.0	62.5	76.2	50.0	61.9	NA		
Shehata 2014 ^[7]	50	50	58.0±6.0	59.0±5.0	70.0	66.0	100.0	100.0	46.0	50.0	Iopromide	6
Ibrahim 2017 ^[9]	50	50	64.8±7.4	62.9±8.3	60.0	70.0	52.0	62.0	60.0	68.0	NA	4
Liu 2015 ^[8]	62	70	59.0±11.2	58.3±10.7	54.8	54.3	61.3	60.0	54.8	54.3	Iodixanol	4
Ye 2017 ^[10]	54	52	63.2±8.3	65.3±8.7	79.6	61.5	NA	NA	79.6	61.5	Iodixanol	6
Rahman 2012 ^[6]	200	200	NA	NA	72.0	86.0	NA	NA	72.0	86.0	NA	4

TMZ: trimetazidine; DM: diabetes mellitus; HT: hypertension; NA: not available.

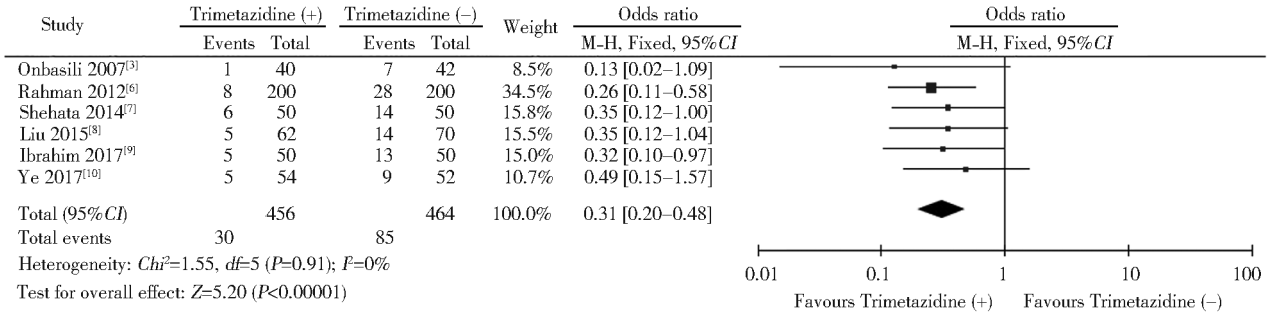


图 2 TMZ (+) 组和 TMZ (-) 组 CIN 发生率的比较

Figure 2 Comparison of CIN incidence between TMZ (+) and TMZ (-) groups

TMZ: trimetazidine; CIN: contrast-induced nephropathy.

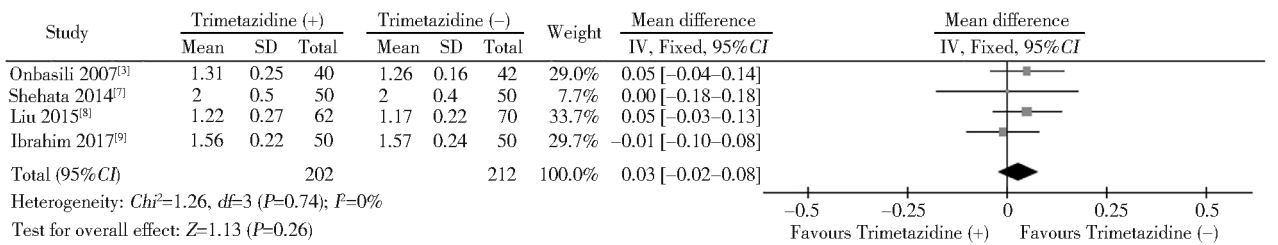


图 3 TMZ (+) 组和 TMZ (-) 组基线血清肌酐值比较

Figure 3 Comparison of baseline serum creatinine values between TMZ (+) and TMZ (-) groups

TMZ: trimetazidine.

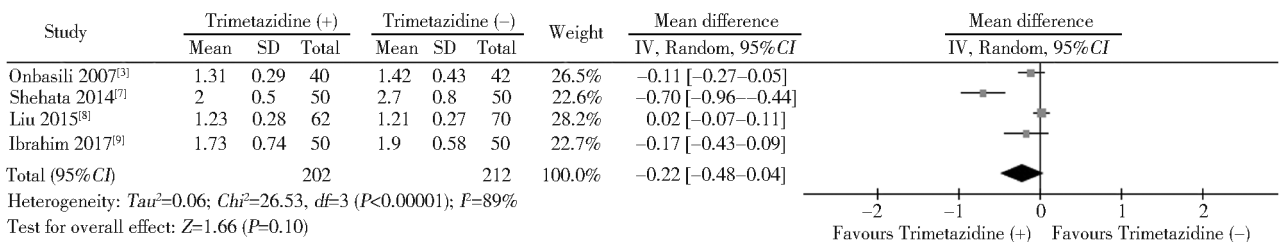


图 4 TMZ (+) 组和 TMZ (-) 组术后 3 d 内血清肌酐值比较

Figure 4 Comparison of serum creatinine values between TMZ (+) and TMZ (-) groups within 3 days after operation

TMZ: trimetazidine.

过相对危险度的对数变换评价发表偏倚,漏斗图的散点呈对称分布,提示不存在发表偏倚。Egger 回归分析证实,各临床终点均无发表偏倚。

3 讨论

本研究发现,与 TMZ(-)组相比, TMZ(+)组的 CIN 发生率显著降低。另外, TMZ(+)组患者 SCr 值在基线水平较 TMZ(-)组高 0.03 mg/ml,而术后 3 d 内却较 TMZ(-)组下降 0.22 mg/ml,虽未达到统计学差异,但仍然提示 TMZ 在预防肾功能不全患者 CIN 发生中起重要作用。

CIN 是冠状动脉造影术后严重的潜在并发症,不仅延长了患者住院时间,甚至还会导致永久性肾功能不全。CIN 发生率与术前肾功能密切相关。据报道^[11],在正常患者人群中 CIN 发生率约 2%,而在晚期肾病患者中可高达 50%。CIN 确切的发生机制尚不明确,可能的机制如下^[12,13]:(1)造影剂直接引起肾血管痉挛,造成肾髓质缺血和缺氧;(2)缺血再灌注后氧自由基的增加导致肾小管损伤;(3)造影剂的高渗透性可引起尿酸盐增加,阻塞肾小管;(4)有效循环血容量减少,肾脏灌注不足。

至今尚无有效的方法预防及治疗 CIN。目前临床上常用的措施包括^[14]:在造影剂使用前后进行充分水化并密切监测肾功能、选择低渗造影剂、术前停用肾毒性的药物(如万古霉素等),以及使用抗氧化类药物(如 N-乙酰半胱氨酸,抗坏血酸和他汀等)。TMZ 是一种哌嗪衍生物,是线粒体长链 3-酰基辅酶 A 的抑制剂。既往大量研究提示 TMZ 在改善肾脏缺血、提高肾功能等方面具有重要作用。Zaoualli^[15]发现 TMZ 通过 Akt/eNOS 信号传导途径的激活、稳定缺氧诱导因子-1 α 及增强血红素加氧酶-1 的活性来提高肾缺血再灌注损伤的耐受性。Park 等^[16]证实 TMZ 能加速缺血性肾脏功能及结构的恢复。此外,张锐等^[17]进行的一项前瞻性随机对照双盲研究结果显示, TMZ 可明显改善休克患者的肾功能。我们本次的荟萃分析证实 TMZ 能降低冠状动脉造影术后患者 CIN 的发生率,佐证了 TMZ 的肾脏保护作用。

既往动物试验与临床研究还证实, TMZ 能降低肾功能损伤后的 SCr 水平,进一步凸显了其肾脏保护作用。如 Kaur 等^[18]研究发现, TMZ 能明显降低肾脏缺血再灌注损伤后大鼠的 SCr 水平。另外, Onbasili 等^[3]及 Ibrahim 等^[9]的研究均表明 TMZ 能显著降低肾功能不全患者冠状动脉造影术后 SCr 水平,防止患者肾功能进一步恶化。本次荟萃分析也

发现,术后 3 d 内 TMZ(+)组患者 SCr 平均水平较 TMZ(-)组下降 0.22 mg/ml,但差异尚未达到统计学意义,考虑与纳入研究数及总体样本量较小有关。

本研究存在一定的局限性:首先,荟萃分析是基于原始数据的二次合并,无法获得患者水平的资料;其次,不同研究对 CIN 的定义及对 SCr 的测定方法并不完全一致,影响了合并结果的可靠性;另外,本次荟萃分析仅纳入 6 项研究,各研究所包含的样本量较少,因而总体患者数量仍较少,研究结论仍有待商榷。

综上所述, TMZ 能显著降低肾功能不全患者 CIN 发生率,故对预防此类患者 CIN 的发生具有积极作用。不过, TMZ 对肾功能不全患者冠状动脉造影术后真实的疗效,尤其是对术后 SCr 水平的影响,仍需要更多高质量、大样本的随机对照研究进一步证实。

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· 消息 ·

致“一带一路”沿线国家和地区医学机构

《中华老年多器官疾病杂志》是由中国工程院院士、老年心脏学专家王士雯教授于2002年创办的全世界唯一一本以老年心脏病和老年心脏病合并其他器官疾病为主要内容的杂志,月刊,由中国人民解放军总医院老年心血管病研究所主办。杂志已被“中国科技论文统计源期刊”(中国科技核心期刊)收录。本杂志的摘要、图表和参考文献,均为中、英文双语对照,方便国外读者顺利阅读。为促进中国与“一带一路”沿线国家和地区的医学及文化交流,本刊将免费刊登其来稿,并赠送当期杂志。欢迎“一带一路”沿线国家和地区的老年心脏病和老年病学医生、学者踊跃投稿。

To medical academic institutions of all countries along the Belt and Road

The Chinese Journal of Multiple Organ Diseases in the Elderly (Zhonghua Laonian Duoqiguan Jibing Zazhi) is founded in 2002 by Shiwen Wang, Member of Chinese Academy of Engineering, a renowned geriatric cardiologist in China. The journal is published monthly by the Institute of Geriatric Cardiology (IGC), Chinese PLA General Hospital in Beijing, China. The journal, the only one in the world currently, focuses on both basic research and clinical practice to the diagnosis and treatment of cardiovascular disease in the aged people, especially those with concomitant disease of other major organ-systems, like the lungs, kidneys, liver, central nervous system, gastrointestinal tract or endocrinology, *etc.* The journal has been listed in the most authoritative Chinese database, the Chinese Scientific and Technical Papers and Citations Database (Chinese Core Sci-Tech Periodical). For convenience of foreign readers, the main parts of the paper, including abstract, tables, figures and references, are expressed in Chinese-English bilingually. To facilitate the cultural and academic communication between China and countries or regions along the Belt and Road, the journal welcomes the manuscripts from these areas. If reviewed qualified, the manuscript would be published without charging, and the authors would receive a complimentary copy of the current issue.

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