Advances in Clinical Medicine 临床医学进展, 2022, 12(2), 1267-1280
Published Online February 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.122185

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非甾体抗炎药联合用药预防经内镜逆行胰胆管造影术后胰腺炎的有效性分析

——一项贝叶斯网状Meta分析

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收稿日期：2022年1月21日；录用日期：2022年2月11日；发布日期：2022年2月24日

摘　要

目的：综合评价直肠100 mg非甾体类抗炎药(NSAIDs)及其组合用药预防经内镜逆行胰胆管造影术后胰腺炎的临床疗效。方法：检索PubMed、Cochrane Library、Embase数据库从建库至2021年7月7日所有关于胰腺炎、经内镜逆行胰胆管造影术(ERCP)、吲哚美辛、双氯芬酸的随机对照试验(RCTs)，根据纳入排除标准筛选文献并提取数据，采用Stata14MP、ADDIS进行数据分析。结果：纳入27项RCTs，术后胰腺炎患者13,496例，8种干预措施。网状Meta分析结果显示单用NSAIDs、高剂量NSAIDs、及NSAIDs组合用药与安慰剂相比在预防经内镜逆行胰腺胆管造影术后胰腺炎均具有显著差异，NSAIDs + 硝酸甘油是预防PEP最好的药物组合(OR = 0.20, 95% CI: 0.09, 0.41)，与单用NSAIDs比较，NSAIDs + 硝酸甘油也有明显预防效果(OR = 0.44, 95% CI: 0.21, 0.92)。概率排序结果显示NSAIDs + 硝酸甘油效果最优，高剂量NSAIDs疗效最弱。与安慰剂比较，单用NSAIDs (OR = 0.37, 95% CI: 0.14, 0.83)在中高风险人群中在预防PEP有效率方面差异有统计学意义。概率排序结果显示NSAIDs + 硝酸甘油在预防PEP有效率上成为最好干预措施的可能性最大(OR = 0.22, 95% CI: 0.03, 1.57)，其次为NSAIDs + 水合作用。结论：8项干预措施中，NSAIDs + 舌下硝酸甘油在总体以及高危人群中消除PEP的疗效明显优于其余药物；NSAIDs + 硝酸甘油、NSAIDs + 水合作用则可能是高危人群的最佳选择。

关键词

经内镜逆行胰胆管造影术，吲哚美辛，双氯芬酸，非甾体抗炎药

Efficacy of Combination of Nonsteroidal Anti-Inflammatory Drugs for Prevention of Pancreatitis after Endoscopic Retrograde Cholangiography

—A Bayesian Network Meta-Analysis

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文章引用: 杜飞, 师恒鑫, 张永烜, 于文昊, 孔繁玉, 王志鑫, 樊海宁, 任利. 非甾体抗炎药联合用药预防经内镜逆行胰胆管造影术后胰腺炎的有效性分析[J]. 临床医学进展, 2022, 12(2): 1267-1280. DOI: 10.12677/acm.2022.122185

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Received: Jan. 21st, 2022; accepted: Feb. 11th, 2022; published: Feb. 24th, 2022

Abstract

Aim: To evaluate the clinical efficacy of 100 mg non-steroidal anti-inflammatory drugs (NSAIDs) and their combination in preventing pancreatitis after endoscopic retrograde cholangiopancreatography. Methods: All RCTs on pancreatitis, endoscopic retrograde cholangiopancreatography (ERCP), indomethacin and diclofenac from the establishment of PubMed, Cochrane Library and Embase databases to July 7, 2021 were searched. Literatures were screened and data were extracted according to inclusion and exclusion criteria. Stata14MP and ADDIS were used for data analysis. Result: A total of 27 Randomized controlled trial (RCTs) met inclusion criteria in the study, including eight interventions in 13,496 patients with post-ERCP pancreatitis (PEP). Results of a network meta-analysis showed significant differences in prevention of PEP between NSAIDs alone, high-dose NSAIDs, NSAIDs combination and placebo. NSAIDs + sublingual nitroglycerin was the best drug combination for PEP prevention (OR = 0.20, 95% CI: 0.09, 0.41), and there was also a statistically significant difference between NSAIDs + nitroglycerin and NSAIDS alone (OR = 0.44, 95% CI: 0.21, 0.92). Probability ranks showed that NSAIDs + sublingual nitroglycerin was the best, while high dose NSAID was the weakest. Compared with placebo, NSAIDs alone (OR = 0.43, 95% CI: 0.21, 0.81) and NSAIDs + hydration (OR = 0.31, 95% CI: 0.07, 0.95) had statistically significant differences in PEP prevention in middle and high-risk groups. Probability ranks showed that NSAIDs + sublingual nitroglycerin was the most likely intervention to prevent PEP effectiveness (OR = 0.22, 95% CI: 0.04, 1.12), followed by NSAIDs + hydration. Conclusion: Among the eight interventions, NSAIDs + nitroglycerin had a better efficacy in eliminating PEP than the other drugs in the general population; NSAIDs + hydration may be the best choice for high-risk groups, as may NSAIDs + nitroglycerin.

Keywords

Endoscopic Retrograde Cholangiopancreatography, Indomethacin, Diclofenac, Nonsteroidal Anti-Inflammatory Drugs

1. 背景和目的

急性胰腺炎是经内镜逆行胰胆管造影术(ERCP)后最常见、较严重的并发症，即使是经验丰富的内镜医师，仍然无法避免其发生。ERCP 术后胰腺炎(PEP)发生率很高，约为 9.7%，死亡率约为 0.7% [1]，其中高危患者中的发病率超过 15%，并且可能造成更高的死亡率[2]。许多 PEP 患者将经历更长的住院时间、更多的治疗干预和额外的医疗费用[3]。针对这一情况，大量的研究正在进行，以期探究预防 PEP 的最佳药物干预措施，大量的研究肯定了非甾体类抗炎药(NSAIDs)预防 PEP 的疗效，作用机制与抑制环氧合酶-2

(COX-2)有关，COX-2 作为炎症级联的一部分而激活，而且 COX-2 在小鼠胰腺炎[4]模型中高表达。目前美国胃肠内镜协会(ASGE)和欧洲胃肠内镜协会(ESGE)已经发布了预防 PEP 的指南[5] [6]，并且推荐直肠 100 mg NSAIDs 作为预防 PEP 基础用药。Serrano 等的一项关于 NSAIDs 的 Meta 分析表明，只有双氯芬酸或吲哚美辛对预防 PEP 有效[7]。同时有研究表明除了在 ERCP 期间使用 NSAIDs 外，术前术后 NSAIDs 均可预防 PEP，且预防效果没有差异[8] [9]。大量的新发布 NSAIDs 及其组合用药(硝酸甘油、水合作用、肾上腺素等)的试验无法确定最优组合，鉴于此，我们希望探究基于直肠 100 mg NSAIDs (双氯芬酸或吲哚美辛)的最优组合用药。

2. 资料与方法

2.1. 纳入及排除标准

2.1.1. 纳入标准

1) 研究类型：安慰剂及直肠 100 mg NSAIDs (吲哚美辛和双氯芬酸)联合用药预防 PEP 的 RCT，且研究中报道了有效率；2) 研究对象：年龄大于 18 岁，且行 ERCP 的患者，无性别、种族、及病因限制；3) 干预措施：安慰剂、直肠单用 100 mg NSAIDs、直肠高剂量 NSAIDs (≥150 mg)、及直肠 100 mg NSAIDs 的组合用药；4) 单组样本量 > 30。

2.1.2. 排除标准

1) 综述、回顾性研究、队列研究等研究类型；2) 非英文以外的文献、重复发表或会议摘要等；3) 除直肠给药以外的其他服药方式(如口服、肌肉注射)；4) 动物试验。

文献检索：在一名经验丰富的专家指导下，有两名研究人员进行独立检索，继而确定最终检索策略。检索数据库包括 PubMed、Cochrane Library、Embase，我们使用了“胰腺炎”“经内镜逆行胰胆管造影术”“吲哚美辛”“双氯芬酸”结合关键词和医学主题标题的搜索策略，检索时间截至 2021 年 7 月 7 日。

2.2. 文献筛选和数据提取

将检索获得的文献导入 EndNoteX9 文献管理软件去重后，由两名评价者按预先制定的纳入、排除标准独立筛选文献，最终确定纳入文献，如有不一致，通过协商或与第三者讨论解决。对纳入文献采用预先制定的资料提取表提取数据，主要内容包括纳入研究的基本信息(作者、年代、样本量、年龄、性别、干预措施)、结局指标(PEP 发生率)和风险偏倚评估(随机分配、隐蔽分组、盲法、结局数据、选择性报告偏倚)。最后两位研究人员进行数据检查，如遇分歧通过讨论解决。

质量评价使用随机对照试验偏倚风险评估工具 ROB 2.0 评估研究质量。在以下方面评估偏倚判断风险：随机化过程引起的偏倚、预期干预偏差引起的偏倚、结果数据缺失引起的偏倚、结局测量的偏倚和选择性报告结果的偏倚。根据偏倚风险的结果，总体偏倚风险被描述为“偏差风险低”、“有些担心”和“偏差风险高”。

2.3. 统计学分析

计数资料采用比值比(OR)，并计算效应量的 95%可信区间(95% CI)。首先进行异质性分析，用 I2 评估异质性，I2 ≤ 50%，则异质性较小可行网状 Meta 分析；否则异质性较大，分析造成异质性的原因，在排除临床异质性因素之后，再进行网状 Meta 分析。使用收敛性评价构建模型的有效性，在 Addis 软件基础设置即 4 条马尔科夫链；初始值为 2.5，退火迭代次数为 20,000，模拟迭代次数为 50,000，细化迭代为 10。迭代轨迹显示模拟采样次数与结果之间的关系，若马尔科夫链条上下波动较小，趋于稳定水平，表明构建的模型具有较好的收敛性。模型能有效地预测数据。为了确保收敛，对潜在尺度减少因子(potential

scale reduction factor, PSRF)进行了评估。若 PSRF ≥ 1.2，说明目前的模拟次数不足以达到很好的收敛，需增加模拟次数；若 PSRF < 1.2 说明已达到收敛，且越接近 1，收敛程度越好。贝叶斯网状 Meta 分析使用 ADDIS 1.16.6 软件进行各个干预异质性、一致性、不一致性及节点分析，最后使用一致性模型结果进行报告，Stata14MP (College Station, Texas USA)及 GraphPad Prism 8 用于分析及作图。严格按照系统评价和网状 Meta 分析报告条目清单[10]进行报告。

2.4. 亚组

对中高危人群进行了亚组分析，定义为至少有一个明确的患者或手术相关的危险因素(患者因素：怀疑 Oddi 括约肌功能障碍、女性、既往胰腺炎、既往 PEP；手术因素：插管困难，导丝插入胰管≥1 次，胰管注射造影剂)或 2 个患者或手术相关危险因素(患者因素：年轻，非扩张肝外胆管，无慢性胰腺炎，血清胆红素正常，终末期肾脏疾病；手术因素：预切术或胰括约肌切开术，胆道球囊扩张，胆管取石失败)[6]。

3. 结果

3.1. 纳入文献的特征和质量评价

根据设定的检索策略和数据收集方法，共检索获得 946 篇文献，排除重复文献 332 篇，根据预先设定的纳入标准排除 586 篇，最终纳入符合标准研究 27 篇，具体流程见图 1。纳入 27 项研究[11]-[37]包含 13,496 名患者和 8 种预防 PEP 的干预措施，涉及安慰剂、单用 NSAIDs、高剂量 NSAIDs、及其组合药物(舌下硝酸甘油、乳酸林格氏液水合作用、静脉生长抑素、十二指肠乳头喷洒肾上腺素、口服褪黑素)，其中 11 项研究报告了中高危人群，纳入研究中基本特征见表 1。图 2 以网络图的形式显示了干预措施之间的直接比较，干预措施节点大小和连接两节点线的粗细与比较的 RCTs 样本量及研究数量成正比。图 3 展示了随机对照试验偏倚风险的评估和汇总。

Table 1. The basic characteristics of the inclusion study
表 1. 纳入研究基本特征

研究	人群	干预			年龄(岁)			性别男/女(n)			PEP (n)		
		组 1	组 2	组 3	组 1	组 2	组 3	组 1	组 2	组 3	组 1	组 2	组 3
Weiland 2021	中高风险	N100mg	N100mg + LR	\	60 (49 - 71)	57 (44 - 71)		175/250	156/232		39	30	
Hosseini 2016*	平均风险	PLA	N100mg		49 ± 14.26 50.76 ± 13.32	51.20 ± 12.12 47.91 ± 11.06		103/102	99/102		27	11	
Lai 2019	平均风险	N100mg	N 高剂量		60.5 ± 16.9	59.3 ± 15.7		47/28	54/33		3	6	
Andrade-Dávila 2015	高风险	PLA	N100mg		54.0 ± 17.85	51.59 ± 18.55		25/59	31/51		17	4	
Döbrönte 2014	平均风险	PLA	N100mg		67.68 ± 15.56	65.66 ± 16.21		133/214	106/212		22	20	
UÇAR 2016	平均风险	PLA	N100mg		60.5 ± 17.6	59 ± 18.6		20/30	13/37		7	1	

Continued

Kamal 2019	高风险	N100mg	N100mg + SE		52.1 ± 14.3	52.5 ± 15.6		201/276	207/275		31	32
Wang 2020	高风险	PLA	N100mg + TI		63.5 ± 14.4	66.87 ± 13		/	/		34	9
Romano-Munive 2021	平均风险	N100mg	N100mg + SE		51.8 ± 20.3	50.3 ± 21.4		87/188	81/192		14	10
Elmunzer 2012	高风险	PLA	N100mg		46.0 ± 13.1	44.4 ± 13.5		66/229	60/247		52	27
Norouzi 2021	高风险	N100mg	N100mg + S		62.95 (15.58)	63.03 (16.57)		86/98	76/116		28	22
Fogel 2019	高风险	N100mg	N 高剂量		49·3 (15·2)	50·4 (15·0)		101/421	123/392		76	65
Hatami 2018	平均风险	N100mg	N100mg + SE		58.06 ± 17.13	59.62 ± 15.37		41/27	24/34		6	0
Sotoudehmanesh 2007	平均风险	PLA	N100mg		58.1 ± 16.8	58.4 ± 17.1		115/130	111/134		15	7
Katsinelos 2012	平均风险	PLA	N100mg + S		68.4 (14.7)	69.2 (15.1)		110/150	122/133		27	12
Khoshbaten 2008	高风险	PLA	N100mg		57 ± 15	60 ± 17		25/25	22/28		13	2
Loza 2007	平均风险	PLA	N100mg		51.12 ±17	55.37 ± 18.0		24/51	26/49		12	4
Lua 2015	中高风险	PLA	N100mg		64.3	64.9		105/118	108/118		11	16
Luo 2016	平均风险	PLA	N100mg		63 (50 - 74)	62 (50 - 72)		619/684	618/679		100	47
Luo 2019	平均风险	N100mg	N100mg + SE		61 (49 - 71)	62 (50 - 71)		295/281	302/280		31	49
Mok 2016	高风险	PLA	N100mg	N100mg + LR	58	62	63	19/29	15/33	25/23	10	6	3
Patai 2015	平均风险	PLA	N100mg		64.51 (20 - 95)	66.25 (23 - 100)		88/181	89/181		37	18
Patil 2016	高风险	PLA	N100mg		47.86	45.44		72/128	77/123		23	6
Masjedizadeh 2017	平均风险	PLA	N100mg		56.25	57.97		28/34	24/38		20	16
Sadeghi 2019	平均风险	N100mg	N100mg + M		58.0 ± 16.8	60.1 ± 14.8		70/70	67/73		19	14
Sotoudehmanesh 2014	平均风险	N100mg	N100mg + TI		58.6 ± 17.5	58.4 ± 17.8		70/80	76/74		23	10
Murray 2003	平均风险	PLA	N100mg		58 ± 14	55 ± 15		36/74	41/69		17	7

PLA：安慰剂或无治疗组；N：吲哚美辛或双氯芬酸；LR：乳酸林格液；SE：十二指肠乳头喷射肾上腺素；TI：舌下硝酸甘油；S：生长抑素；M：褪黑素。

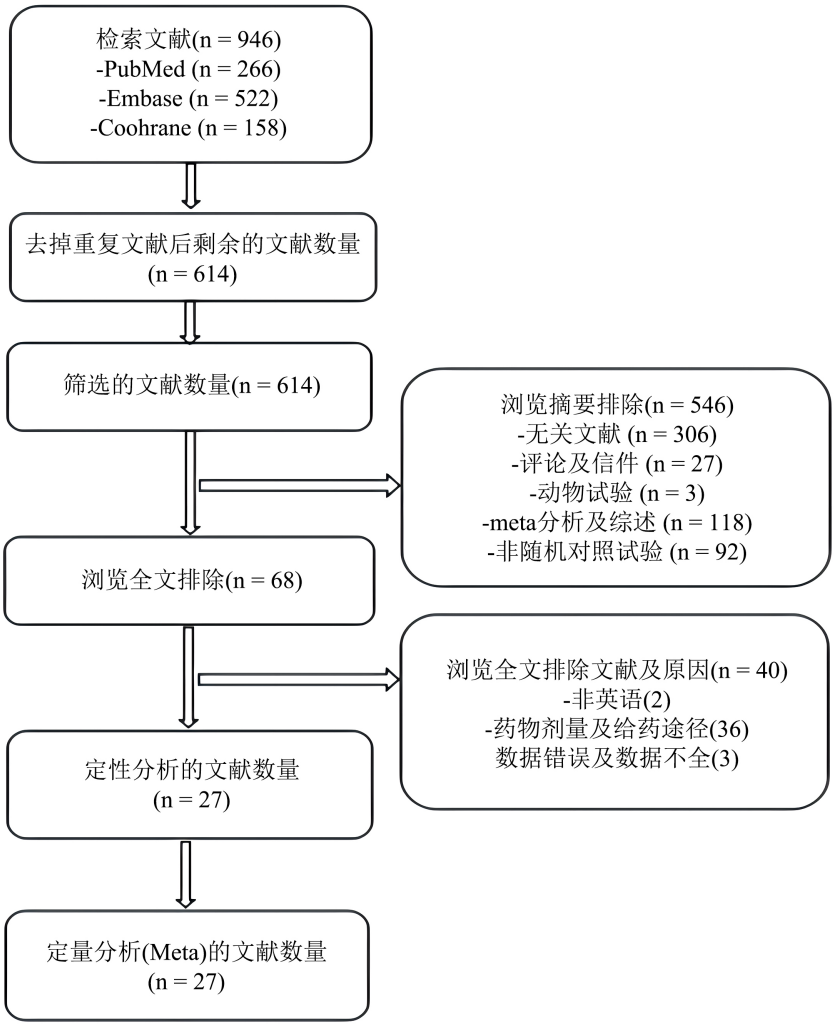


Figure 1. Flow diagram of literature screening
图 1. 文献筛选流程图

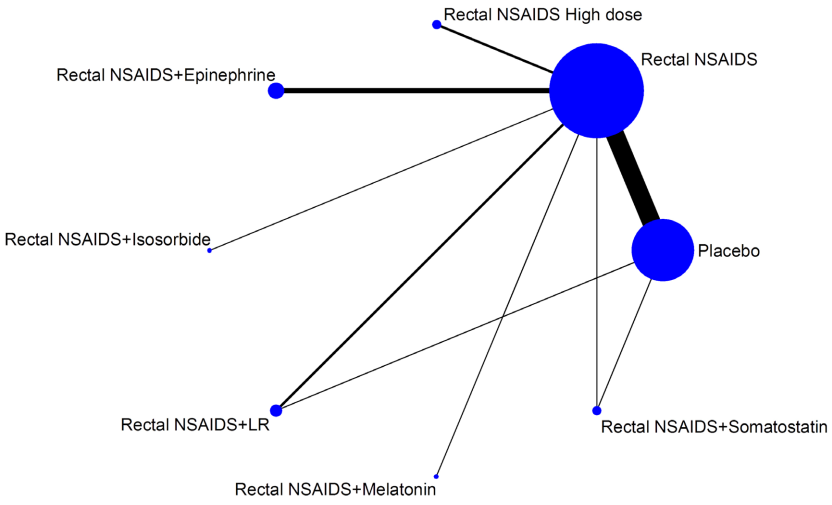
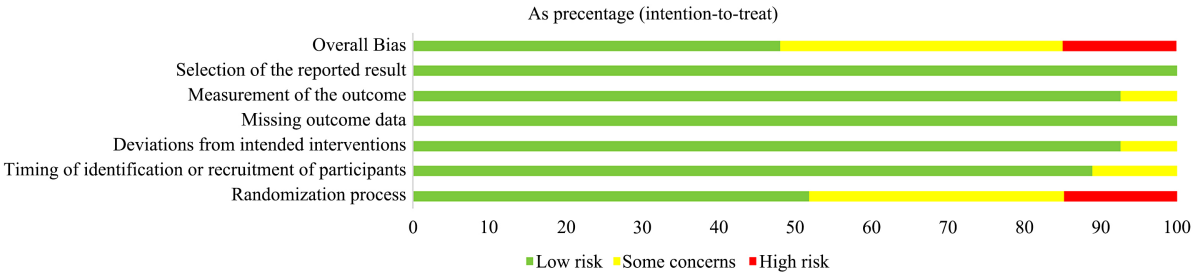
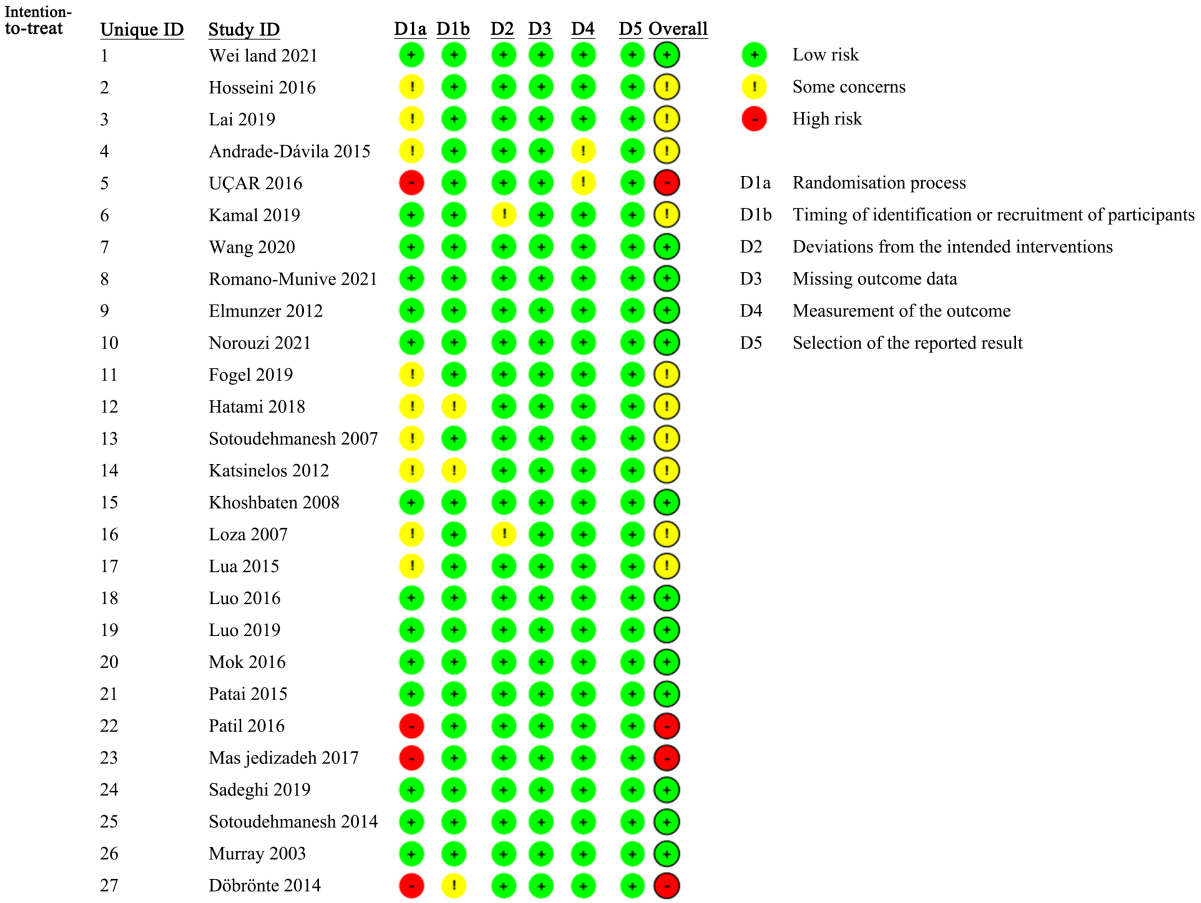


Figure 2. Network evidence plots for interventions in average-risk population
图 2. 网状关系图



(a)



(b)

Figure 3. (a) Bias risk diagram of RoB2; (b) Summary chart of bias risk of RoB2
图 3. (a) RoB2 风险偏倚图；(b) RoB2 风险偏倚汇总图

3.2. 网状 Meta 分析结果

3.2.1. 总体人群网状 Meta 结果

共有 27 项研究报告了包含纳入标准的药物组合预防 PEP 的有效率，异质性检验提示不同干预间异质性(I2 < 50%)可接受，闭合环同质性良好($\zeta^2 < 0.05$)，ADDIS 基础设置下马尔科夫链波动小，迭代轨迹稳定，且结局指标的 PSRF 均为 1，表明模型具有良好的收敛性，可以有效地预测数据。基于一致性模型的贝叶斯网状 meta 结果表明，与安慰剂比较，单用 NSAIDs、高剂量 NSAIDs、及 NSAIDs 的组合用药预防 PEP 存在统计学意义的差异，NSAIDs + 硝酸甘油是预防 PEP 最好的药物组合(OR = 0.20, 95% CI:

0.09, 0.41)，与单用 NSAIDs 比较，其也有明显的效果(OR = 0.44, 95% CI: 0.21, 0.92)，其他组合用药以及高剂量 NSAIDs 均未见统计学意义的差异(表 2)。概率排序结果显示 NSAIDs + 硝酸甘油成为预防 PEP 最好干预措施的可能性最大，其次为 NSAIDs + 褪黑素、NSAIDs + 水合作用、NSAIDs + 生长抑素、单用 NSAIDs、NSAIDs + 肾上腺素、高剂量 NSAIDs、安慰剂(图 4)。

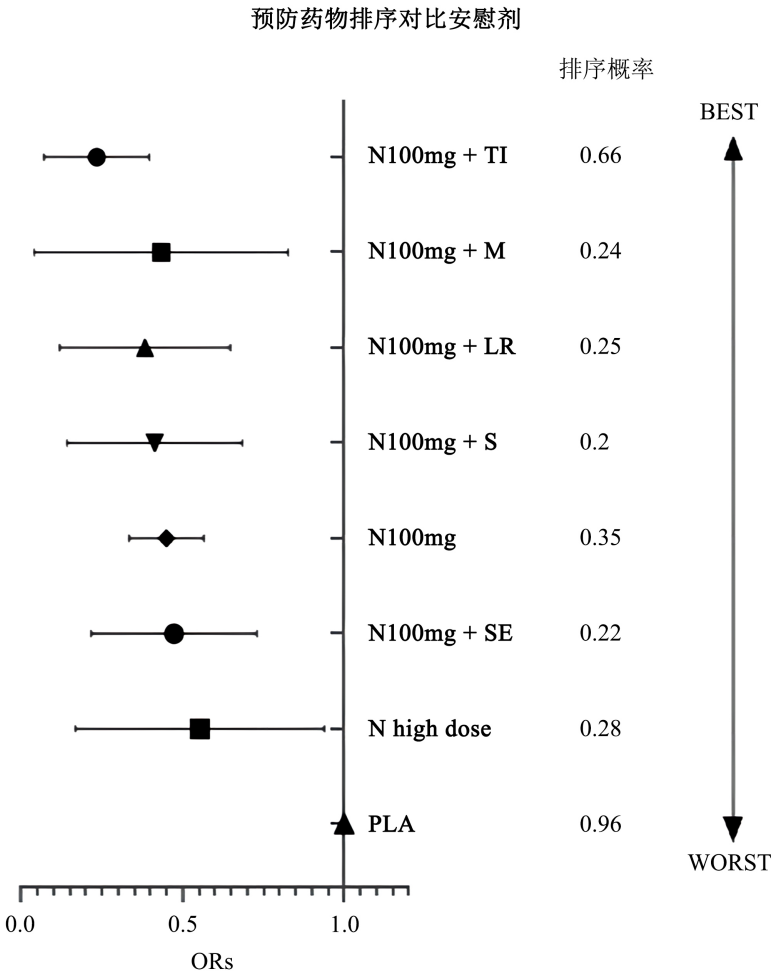


Figure 4. Probability ranking chart of total population
图 4. 总体人群概率排序图

3.2.2. 中高风险人群网状 Meta 结果

共有 11 项研究报告了中高风险人群。基于网状 Meta 结果，与安慰剂比较，单用 NSAIDs (OR = 0.37, 95% CI: 0.14, 0.83)在预防 PEP 方面效果显著(表 3)。概率排序结果显示 NSAIDs + 硝酸甘油在预防 PEP 有效率上成为最好干预措施的可能性最大(OR = 0.22, 95% CI: 0.04, 1.12)，其次 NSAIDs + 水合作用。

总之，预防 PEP 的主要结果中，NSAIDs + 硝酸甘油在总体和高危人群中被选为最佳用药组合的可能性最高(71%)。NSAIDs + 水合作用(25%)则可能是高危人群的另一较好选择。

3.2.3. 网状 Meta 分析收敛性、一致性与不一致性

在 ADDIS 默认设置之下模型显示一致性良好，不存在不一致性；节点模型分析也显示不存在不一致性见表 4。

Table 2. Results of Bayesian network Meta analysis of different interventions
表 2. 不同措施的贝叶斯网状 Meta 分析结果

结果	PLA	N100mg	N 高剂量	N100mg + SE	N100mg + TI	N100mg + LR	N100mg + M	N100mg + S
PEP 发生率(Ors)								
PLA	1	**0.44 (0.34, 0.57)**	**0.45 (0.23, 0.98)**	**0.45 (0.23, 0.74)**	**0.20 (0.09, 0.41)**	**0.33 (0.15, 0.67)**	**0.32 (0.11, 0.87)**	**0.35 (0.18, 0.71)**
N100mg	**2.25 (1.77, 2.98)**	1	1.00 (0.55, 2.16)	1.02 (0.56, 1.58)	**0.44 (0.21, 0.92)**	0.74 (0.36, 1.47)	0.71 (0.26, 1.94)	0.79 (0.41, 1.61)
N 高剂量	**2.24 (1.02, 4.32)**	1.00 (0.46, 1.81)	1	1.02 (0.36, 2.07)	0.44 (0.15, 1.11)	0.74 (0.25, 1.80)	0.71 (0.20, 2.23)	0.79 (0.29, 1.99)
N100mg + SE	**2.22 (1.35, 4.40)**	0.98 (0.63, 1.77)	0.98 (0.48, 2.79)	1	0.44 (0.19, 1.15)	0.73 (0.32, 1.82)	0.70 (0.25, 2.32)	0.78 (0.36, 2.09)
N100mg + TI	**5.11 (2.44, 11.22)**	**2.27 (1.09, 4.84)**	2.28 (0.90, 6.79)	2.29 (0.87, 5.37)	1	1.69 (0.61, 4.67)	1.61 (0.47, 5.60)	1.80 (0.69, 4.97)
N100mg + LR	**3.06 (1.49, 6.67)**	1.36 (0.68, 2.81)	1.35 (0.56, 4.00)	1.37 (0.55, 3.12)	0.59 (0.21, 1.65)	1	0.97 (0.29, 3.42)	1.07 (0.42, 3.00)
N100mg + M	**3.15 (1.14, 9.23)**	1.40 (0.52, 3.86)	1.40 (0.45, 4.99)	1.42 (0.43, 4.05)	0.62 (0.18, 2.14)	1.03 (0.29, 3.44)	1	1.10 (0.35, 3.95)
N100mg + S	**2.85 (1.41, 5.63)**	1.26 (0.62, 2.44)	1.27 (0.50, 3.42)	1.28 (0.48, 2.75)	0.56 (0.20, 1.45)	0.93 (0.33, 2.40)	0.91 (0.25, 2.89)	1

Table 3. Results of Bayesian network Meta analysis of different interventions in high-risk group
表 3. 中高风险组不同措施的贝叶斯网状 Meta 分析结果

结果	PLA	N100mg	N 高剂量	N100mg + SE	N100mg + TI	N100mg + LR	N100mg + S
PEP 发生率(Ors)							
PLA	1	**0.37 (0.14, 0.83)**	0.32 (0.04, 2.16)	0.38 (0.04, 3.06)	0.22 (0.03, 1.57)	0.26 (0.05, 1.08)	0.27 (0.03, 2.19)
N100mg	**2.68 (1.20, 6.90)**	1	0.84 (0.13, 5.80)	1.01 (0.14, 7.63)	0.57 (0.07, 5.36)	0.69 (0.15,2.65)	0.72 (0.10, 5.45)
N 高剂量	3.17 (0.41, 26.02)	1.19 (0.17, 7.83)	1	1.19 (0.08, 21.01)	0.69 (0.03, 13.02)	0.83 (0.07, 8.10)	0.87 (0.05, 14.30)
N100mg + SE	2.62 (0.33, 24.97)	0.99 (0.13,7.23)	0.84 (0.05, 13.03)	1	0.56 (0.03, 12.03)	0.68 (0.05, 7.37)	0.71 (0.04, 12.07)
N100mg + TI	4.60 (0.64, 36.70)	1.75 (0.19, 14.95)	1.46 (0.08, 28.47)	1.78 (0.08, 33.00)	1	1.21 (0.08, 13.49)	1.25 (0.06, 24.61)
N100mg + LR	3.86 (0.93, 21.43)	1.45 (0.38, 6.85)	1.21 (0.12, 14.46)	1.46 (0.14, 19.23)	0.82 (0.07, 11.91)	1	1.04 (0.09, 13.38)
N100mg + S	3.64 (0.46, 37.55)	1.38 (0.18, 10.38)	1.15 (0.07, 19.44)	1.40 (0.08, 24.24)	0.80 (0.04, 16.95)	0.96 (0.07, 11.76)	1

PLA：安慰剂或无治疗组；N：吲哚美辛或双氯芬酸；LR：乳酸林格液；SE：十二指肠乳头喷射肾上腺素；TI：舌下硝酸甘油；S：生长抑素；M：褪黑素。

Table 4. Analysis of total population node model
表 4. 总人群节点模型分析结果

研究名称	直接结果	间接结果	总体	Z 检验 P 值
PLA, N100mg	−0.81 (−1.12, −0.57)	−0.80 (−1.59, 0.04)	−0.81 (−1.09, −0.57)	0.98
PLA, N100mg + TI	−1.48 (−2.58, −0.53)	−1.77 (−2.86, −0.69)	−1.63 (−2.42, −0.89)	0.64
PLA, Rectal NSAIDS + LR	−1.48 (−3.11, −0.08)	−0.97 (−1.88, −0.15)	−1.12 (−1.90, −0.40)	0.53
PLA, N100mg + S	−0.88 (−1.87, 0.09)	−1.19 (−2.10, −0.23)	−1.05 (−1.73, −0.34)	0.61
N100mg, N100mg + TI	−0.93 (−1.98, 0.06)	−0.67 (−1.79, 0.37)	−0.82 (−1.58, −0.09)	0.72

PLA：安慰剂或无治疗组；N：吲哚美辛或双氯芬酸；LR：乳酸林格液；TI：舌下硝酸甘油；S：生长抑素。

4. 讨论

本研究中，与其他干预相比，NSAIDs 联用硝酸甘油是预防 PEP 最有效的干预措施，并且其相比较单用 NSAIDs 也有统计学差异。对于高危患者，NSAIDs 联合水合作用则可能是高危人群的最佳选择，存在统计学差异，但是这也不能掩盖 NSAIDs 联用硝酸甘油成为最佳药物组合的可能性。我们的结果突出了组合用药在预防 PEP 方面发挥的重要作用。最近的一项网状 meta 分析[38]也证明了类似的结果，直肠吲哚美辛联合水合作用与直肠双氯芬酸联合舌下硝酸甘油是预防 PEP 最有效的联合方案，但其未限定 NSAIDs 的剂量，而我们的研究限定剂量为 100 mg。舌下硝酸甘油已被证明可以降低 PEP 发生率，但是对于降低 PEP 严重程度几乎无帮助，这也是目前 ESGE 指南推荐的干预措施。因为硝酸盐是平滑肌弛缓剂，可放松 Oddi 括约肌并增加胰腺实质的血流量[39]，也许硝酸甘油与 NSAIDs 具有协同效应。在我们这项研究中，无论对于平均风险还是中高风险，直肠 NSAIDs 联用舌下硝酸甘油概率排名均为第一，相信随着更多随机对照试验的进行，可以为这一结果提供更多的证据。水合作用已被证实是一种预防胰腺炎的措施[40]。本研究结果与 Radadiya [9]等报告组合水合作用可能是中高风险的最佳药物预防策略相一致，但这项研究纳入了胰管支架组，并认为胰管支架是最佳选择。水合作用衍生出了积极水合(即 ERCP 开始 60 分钟内静脉滴注 20 ml/kg 的林格乳酸溶液，然后 3 ml/kg/h 持续 8 小时)，但是最近的一项多中心的随机对照试验报道在常规接受预防性 NSAIDs 的中至高危患者中，手术前后积极水化并不能降低 PEP 的发生率[10]，还需要高质量的试验来证明其对 PEP 的预防效果。我们的研究似乎也证实了联用肾上腺素预防 PEP 没有益处，尽管肾上腺素在单用时或许表现了一定的效果，但是在合用药物中却没有额外的预防效果[41] [42] [43]。究其原因可能与喷洒肾上腺素后胰腺实质血供减少有关，进而抑制 NSAIDs 的局部药物浓度，从而拮抗其有益作用；其次，肾上腺素与直肠 NSAIDs 药理作用可能存在拮抗作用[29]。高剂量 NSAIDs 的排名更加靠后，以及结合当前证据基本否认了高剂量 NSAIDs 在预防 PEP 中的作用，正如 Rana 所说高剂量并不一定是好的[44]。我们的研究仍然存在不足，根据研究设定我们对标准水合作用以及积极水合作用未做分类，这样可能无法确定积极水合的疗效，尽管在一项比较标准水合以及积极水合预防 PEP 的试验中，预防性联合使用 NSAIDs 和积极水合作用没有降低 PEP 的发生[45]。综上所述，本研究将 8 项干预措施预防 PEP 的疗效进行比较，NSAIDs 联用硝酸甘油和水合作用的效果较优，尚需大样本、高质量的随机对照试验进一步分析。

数据声明

我们的数据可以获取。

利益冲突声明

本研究不存在研究者、伦理委员会成员、受试者监护人以及与公开研究成果有关的利益冲突。

作者贡献声明

樊海宁、任利、杜飞、师恒鑫负责课题设计，师恒鑫和杜飞完成了文献检索和文献筛选，于文昊和张永烜完成了数据提取，师恒鑫和杜飞完成了文献质量评价，王志鑫和杜飞负责数据分析，杜飞和孔繁玉绘制了表格。手稿撰写由杜飞完成，樊海宁和任利对手稿进行了修改，所有作者都查看了手稿，并同意发表。

试验注册

注册机构：INPLASY—International Platform of Registered Systematic Review and Meta-analysis Protocols

注册号：INPLASY2021100086

基金项目

青海省高端创新人才千人计划；2020 年度青海省“昆仑英才”行动计划。

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