

Combining Thrombolysis in Myocardial Infarction risk score and clear-cut alternative diagnosis for chest pain risk stratification

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Background

- TIMI score (Thrombolysis in myocardial infarction) 是預測病患死亡或嚴重心血管預後的scoring system
- 病人出院後的outcome是關注的焦點。
- 本實驗在討論低TIMI score是否可以作為病人低不良預後的指標。

Method

- Setting: Hospital of the University of Pennsylvania
- Population:
 - >30歲，在就診之初被懷疑可能為有急性冠心症的急診病人。
 - 實驗助理在07:00~24:00這段時間內篩選出符合條件的個案，這段時間來診病人佔該單位85%~95%的病患數。
 - 講英文(95%病人)
- 資料蒐集：
 - 在初步survey後，醫師要回答該病患是否有其他更可能的診斷。
 - 所以病人，除死亡外，均follow 30天。
- 主要預後：
 - 病患30-day 心血管病事件(death, revascularization, CABG)
 - 出院後30-day adverse event <1%預設為可接受的threshold

Table 1 Characteristics of patients stratified by presence or absence of alternative diagnosis

Patient characteristics	Alternative diagnosis (n = 991)		No alternative diagnosis (n = 2178)		P
	n	%	n	%	
Age (y)	51.2 ± 15.0		54.7 ± 14.1		
Sex (female)	553	59	1124	54	.01
Race					.16
Black	645	69	1370	66	
White	258	28	645	31	
Other	34	4	69	3	
Pain duration (IQR)	300 min (20-2880)		120 min (15-550)		<.01
Pain onset before ED arrival (IQR)	720 min (120-2880)		240 min (60-960)		<.01
Cardiac risk factors					
Hypertension	455	48	1316	63	<.01
Diabetes	164	17	474	23	<.01
Elevated cholesterol level	185	20	671	32	<.01
Family history of CAD	93	10	341	16	<.01
Tobacco use	359	38	891	43	.02
TIMI risk factors					
Age >65 y	178	19	481	23	.01
Known coronary disease	100	11	490	23	<.01
>3 cardiac risks factors	188	20	647	31	<.01
Aspirin use in past wk	202	22	800	38	<.01
2 or more episodes of angina	141	15	773	37	<.01
ST-segment deviation	23	2	118	6	<.01
Elevated cardiac markers	27	3	115	6	<.01
Prior stress testing	177	19	725	35	<.01
Abnormal findings	22	12	146	20	.04
Prior catheterization	123	13	536	26	<.01
Abnormal findings	45	36	279	52	<.01
Initial ECG interpretation					
Normal/nonspecific	806	86	1593	76	<.01
Abnormal/nondiagnostic	72	8	188	9	
Ischemia/MI	59	6	308	15	

CAD indicates coronary artery disease; ECG, electrocardiogram; IQR, interquartile range; MI, myocardial infarction.

Adverse event rate

Table 2 Relationship between TIMI score and presence or absence of alternative diagnosis with respect to triple composite outcome

TIMI score	Alternative diagnosis	No alternative diagnosis
0	13/443 (2.9)	11/537 (2.0)
1	14/268 (5.5)	24/560 (4.3)
2	13/133 (9.8)	32/447 (7.2)
3	8/63 (12.7)	39/285 (13.7)
4	3/24 (12.5)	48/199 (24.1)
5-7	1/8 (12.5)	23/50 (46.0)

Values are expressed as n (%).

Table 3 Relationship between TIMI score and presence or absence of alternative diagnosis with respect to individual outcomes

TIMI score	Alternative diagnosis	In-hospital			30-d outcomes		
		Death	MI	Revasc	Death	MI	Revasc
0	Yes (n = 443)	8 (1.8)	1 (0.2)	1 (0.2)	0	12 (2.7)	0
	No (n = 537)	0	6 (1.1)	4 (0.7)	0	2 (0.4)	0
1	Yes (n = 268)	3 (1.1)	3 (1.1)	2 (0.8)	0	9 (3.4)	1 (0.3)
	No (n = 560)	0	16 (2.9)	12 (2.1)	0	1 (0.2)	2 (0.4)
2	Yes (n = 133)	3 (2.2)	6 (6.0)	3 (2.2)	0	5 (3.8)	1 (0.8)
	No (n = 447)	0	18 (4.0)	13 (2.9)	2 (0.4)	4 (0.9)	2 (0.4)
3	Yes (n = 63)	3 (4.8)	4 (6.3)	1 (1.6)	0	5 (3.8)	1 (0.8)
	No (n = 285)	2 (0.7)	18 (6.3)	25 (8.8)	1 (0.3)	4 (1.4)	5 (1.1)
4	Yes (n = 24)	0	2 (8.3)	0	0	2 (8.3)	0
	No (n = 199)	4 (2.0)	23 (11.6)	35 (17.6)	3 (1.6)	5 (2.5)	3 (1.5)
5-7	Yes (n = 8)	0	0	0	0	0	1 (12.5)
	No (n = 61)	0	26 (42.6)	18 (29.5)	2 (3.3)	0	1 (1.6)

Revasc indicates revascularization.

Conclusion

- 高TIMI score的病人如果favor其他診斷時，其30-day CV event發生率較維持ACS診斷者有明顯的降低；儘管如此，其發生率仍>10%。
- 低TIMI score(TIMI score 0 or 1) 病人，無論有無alternative診斷，30-day adverse CV event的發生率無明顯差異。
- 低TIMI score加上有其他非ACS臨床臆斷的病人，仍有2.9%(95%CI 1.6%~5.0%)的不良CV event

Discussion

- TIMI score起初是拿來用在UA/NSTEMI身上，預測14天內的Adverse CV event，現在被擴大解釋，用來預測急診病人回家之後的不良預後。
- 之前有研究已指出低TIMI score不能拿來當作安全放病人回家的依據。
- Hollander et al 提出: strong clinical impression of clear cut alternative Dx可當作急診安全放病人回家的依據。但不良預後發生率還是有4%。
- 本文想加入clinical alternative diagnosis這一參數來看是否可以增加低TIMI score的negative predict value；但顯然是失敗的。
- Low TIMI score group中，有alternative diagnosis者回家後的MI發生率還比無alternative Dx者高!?

Discussion

- 現行protocol是住院或在Chest pain OBS unit觀察8~12小時。
- 有小研究[2]指出coronary CTA可當作一個快速且安全放病人回家的依據。
- 作者表示，儘管Clinical impression和TIMI score都可以做risk stratification，但無論是哪一種或合併起來使用，都無法使病人出院的不良預後率降到理想目標(<1%)

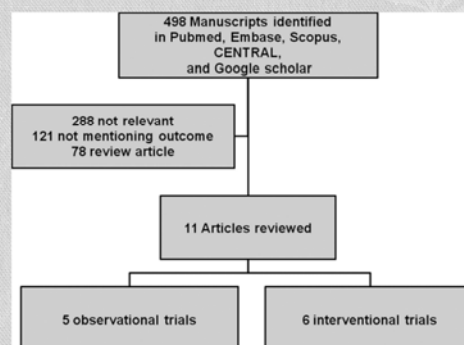
Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*

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Background

- 在Septic shock patient最常用的vasopressor: Dopamine & norepinephrine
 - 兩者都會作用在 α -adrenergic receptor，產生vasopressor作用；但dopamine的 α 作用較弱，反而 β receptor的作用較強
 - Dopamine的 β adrenergic作用可增加cardiac output，但也會增加hear rate與arrythmia的機會，增加cell metabolism，甚至降低免疫功能
- 現行guideline一線vasopressor建議norepinephrine與dopamine但並沒有特別偏好何者。
- 一些觀察型的研究發現使用dopamine的shock病人較使用norepinephrine者差[1]
- 有大型randomized trial[2]指出使用兩者的outcome差不多，但dopamine組的arrythmia機會較高



Result

Table 1. Characteristics of observational studies

First Author (Year)	Type of Comparison	Dopa/Norepi (n = 562/798)	Exposure Time	Mortality Rates
Martin (2000) (11)	Norepi vs. others	40/57	NA ^a	28-day + hospital
Hall (2004) (24)	Dopa vs. norepi	51/49	NA ^a	28-day
Sakr (2006) (3)	Dopa vs. others (norepi mostly)	174/292	NA ^a	Intensive care unit + 30-day + hospital
Povoa (2009) (13)	Dopa or norepi vs. others	231/334 ^b	NA ^a	Hospital
Boulain (2009) (12)	Dopa vs. others (norepi mostly) matched pairs	66/66	NA ^a	Intensive care unit + 28-day + hospital

Result

Study	Norepinephrine		Dopamine		RR [95%CI]	Dopa/norepi
	Event	Total	Event	Total		
Martin et al.	35	57	34	40	1.38 [1.09-1.77]	
Hall et al.	32	49	31	51	0.93 [0.69-1.26]	
Sakr et al.	124	292	95	174	1.29 [1.06-1.56]	
Povoa et al.	174	334	89	231	0.74 [0.61-0.90]	
Boulain et al.	35	66	44	66	1.26 [0.95-1.67]	
Overall	400	798	293	562	1.08 [0.84-1.41]	

Result

Table 2. Characteristics of interventional studies

	Martin (1993) (27)	Marik (1994) (30)	Ruokonen (2003) (29)	Mathur (2007) (25)	Patel (2010) (16)
Dopamine, n	16	10	5	25	134
Norepinephrine, n	16	10	5	25	138
Exposure time	Weaning or dead	3 hrs	3 hrs	6 hrs	Maximum 28 days
Mortality rate	Hospital	Not defined	Not defined	Not defined	28 day ^a
Cochrane risk of bias in included studies					
Concealment on allocation	No	Yes	No	No	Yes (odd or even)
Inclusion/exclusion	Yes	Yes	Yes	Yes	Yes
Patient description	No	No	No	Yes	Yes
Similar care	Yes	No	No	Yes	Yes
Blinding of caregivers	No	No	No	Yes	No
Blinding of assessors	No	No	No	Yes	No
Intention to treat	Yes	Yes	Yes	Yes	Yes
Free from selective reporting	Yes	Yes	Yes	Yes	Yes
Risk of bias for secondary outcomes assessment in included studies					
Adverse events					
Defined	No	No	No	No	Yes
Assessed	No	No	No	No	Yes
Time of assessment	No	No	No	No	Yes
Organ function					
Defined	No	No	No	Yes	Yes
Assessed	No	No	No	Yes	Yes
Time of assessment	No	No	No	Yes	Yes

Result

Study	Norepinephrine		Dopamine		RR [95%CI]	RR Dopa/norepi
	Event	Total	Event	Total		
Martin et al.	7	16	10	16	1.43 [0.73-2.80]	
Marik et al.	5	10	6	10	1.20 [0.54-2.67]	
Ruokonen et al.	4	5	3	5	0.75 [0.32-1.74]	
Mathur et al.	14	25	19	25	1.36 [0.90-2.05]	
De Backer et al.	249	502	291	542	1.08 [0.98-1.19]	
Patel et al.	51	118	67	134	1.16 [0.89-1.51]	
Overall	330	676	396	732	1.12 [1.01-1.20]	

Conclusion

- Observation study group 結果的歧異性較高 (RR 1.09, 95%CI 0.84~1.41, p=0.72)，剔除掉歧異性最高的study後dopamine和norepinephrine的治療預後仍有統計學意義 (RR 1.23, 95%CI 1.05~1.43, p < 0.01)。
- Intervention group的歧異性低，結果顯示dopamine group的outcome較差 (RR 1.12, 95%CI 1.01~1.20, p=0.035)
- 住院天數無統計學意義的差異：
 - ICU (RR -0.3; 95%CI -1.5~1.0; p=0.67)
 - Hospitalization (RR 0.0; 95%CI -2.8~2.6; p=0.95)
- Mortality以外的其他adverse event/outcome只有 De backer[2]的研究有記錄

Discussion

- 許多study裡都不止使用一種vasopressor，也沒有記載使用時間長短，造成無法評估個別vasopressor在治療上影響的程度。
- 會使用norepinephrine的病人跟使用dopamine者的特性本身即可能不同，選用norepinephrine者很可能更著眼於其較強的vasopressor能力。
- 在剔除極端歧異性的研究後，無論observation studies or interventional studies都指向dopamine group預後較差。
- 還是有limitation:
 - Intervention組幾乎都有hemodynamic endpoint：可能換藥
 - 大家定義outcome時間點不同：最後就拉長到28day為outcome endpoint
 - De backer這組study有追蹤到1year的outcome (1.15, 0.91~1.46)，不過只有他追蹤最久，因此沒辦法做長期預後的討論。

Reference

- [1] *Dopamine therapy in septic shock: Detrimental effect on survival?* Boulain T, Runge I, Bercault N, et al: J Crit Care 2009; 24: 575–582
- [2] *Comparison of dopamine and norepinephrine in the treatment of shock.* De Backer D, Biston P, Devriendt J, et al: N Engl J Med 2010; 362:779–789