EFFECT OF PENTOXIFYLLINE ON RENAL OUTCOMES IN CHRONIC KIDNEY DISEASE PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Chronic kidney disease (CKD) represents an important health problem worldwide and the search for new therapeutic approaches for retarding CKD progression is a timely issue. Recent evidence suggest that the antiinflammatory and hemorrheologic agent Pentoxifylline (PTX), may produce favorable effects on kidney function. In order to investigate whether PTX derivatives, alone or in combination to other treatments, may be useful in slowing down disease progression in patients with diabetic or non-diabetic CKD, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs).

		Pento	difylline		other treatr	nent	.		Mean Difference	Mean Difference
tudy or Subgroup	IV	lean [g/24h]	SD [g/24h]	Total Mea	n[g/24h] SD[g/24h]	Total N	Veight	IV, Random, 95% CI [g/24h]	IV, Random, 95% CI [g/24h]
minorroaya 2005		1	U.7	20	0.8	0.7	19	7.3%	0.20 [-0.24, 0.64]	
ladri 2013		1.36	0.82	12	1.98	0.96	6	3.6%	-0.62 [-1.52, 0.28]	
horbani 2012		0.2	0.16	44	0.52	0.31	50	10.6%	-0.32 [-0.42, -0.22]	*
ouerrero-Romero IDDM-PR	DT 1995	0.15	0.09	13	0.6	0.1	10	10.7%	-0.45 [-0.53, -0.37]	•
uerrero-Romero NIDDM-PF	ROT 1995	0.05	0.025	12	0.85	0.24	10	10.3%	-0.80 [-0.95, -0.65]	+
in-Lei 2012		2.1	1.3	16	2.4	1.2	16	3.7%	-0.30 [-1.17, 0.57]	+
avarro 1999		1.63	1.1	14	3.7	1	10	3.9%	-2.07 [-2.92, -1.22]	
avarro 2003		0.8	0.5	30	0.8	0.48	15	8.8%	0.00 (-0.30, 0.30)	_ _ _
diaei 2011		0.68	0.72	28	0.8	0.5	28	8.6%	-0.12[-0.44]0.20]	
antoia 2003		4.7	2.12	7	2.0		7	1 4 96		
arkine 2000 arkine 2000		7.5	1	17	270	1/12	។ 16	37%	-0.02 [-0.04, 0.05]	
ernina 2003 Joo r hob 2010		2.00	1 00	11 75	J.20 2.02	1.40	10	0.7 N 0.7 N		
		1.31	1.02	30 40	2.02	1.09	30 44	0.7%	-0.71 [-1.20, -0.22]	
olente 1987		0.75	0.22	10	0.8	0.23	11	9.9%	-0.05 [-0.24, 0.14]	Т
nang 2001		0.12	0.04	66	0.13	0.05	40	10.9%	-0.01 [-0.03, 0.01]	Ī
otal (95% Cl)				324			273 [~]	00.0%	-0.33 [-0.54, -0.13]	•
eterogeneity: Tau² = 0.10; C	≿hi²= 284.73, c	lf = 13 (P ≤ 0.0	0001); l ² =	95%						
est for overall effect: Z = 3.1	7 (P = 0.002)									Favours (pentoxifylline) Favours (control)
ig.2 – Effects of	f pentoxi	ifvlline v	vs. cor	trol trea	atment o	n uri	narv	albu	umin excretion	
8	Pento	oxifylline		other	treatment		J		Mean Difference	Mean Difference
udy or Subgroup M	lean [µg/min]	SD [µg/min]	Total M	ean [µg/min]	SD [µg/min]	Total	Weigh	t IV, R	andom, 95% Cl [µg/min]	IV, Random, 95% Cl [µg/min]
ura 1998	36.3	31	7	39.8	49.82	7	7.79	<u>,</u>	-3.50 [-46.97, 39.97]	
nicoechea 2012	350.7	 530 6	46	120.1	199.0	1 45	0.89	-	230 60 (65 10 306 01)	
ormankava 2002	000.1	0.00.0	70 26	100.1	100.0	 	0.07 07 70	0 (
annankaya 2003 	00.9 540.0	0.J 400 C	20	102.70	· 10.42	. 20 . 94	4 70	0 /		
avarro 2005	549.3	189.6	30	625	. 238.2	: 31	1.79	0	-75.70[-183.56, 32.16]	
REDIAN 2015	897.2	831.2	82	934.7	787.5	6 87	0.4%	6	-37.50 [-281.94, 206.94]	
odriguez-Moran 2005	23.1	6.5	62	23.9	ı 2.8	61	23.29	6	-0.80 [-2.56, 0.96]	•
plerte 1987	327	116	10	369	ı 133	: 11	1.89	6	-42.00 [-148.52, 64.52]	
ang 1999	63.7	8.8	38	91.2	: 8.9	ı 39	22.99	6	-27.50 [-31.45, -23.55]	•
nang 2001	55.82	27	66	75.62	43.34	. 40	18.89	6	-19.80 [-34.73, -4.87]	+
vtal (05% CI)			366			346	100.00	۷.	14 05 [29 70 0 60]	
nai (35% ci) otorogonoity: Touž – 242 6.	4: ∩hi≅ – 160 (0.000013	IZ - 0.5%		540	100.03	0	- 14.05 [-20.75, 0.05]	• • • • •
est for overall effect: Z = 1.8	4, Chi = 100.8 37 (P = 0.06)	or,ui=o(i s	0.000017,	1 - 35 %						-200 -100 Ó 100 200
	C t	: C _11:		4						Favours (Pentoxitylline) Favours (control)
1g.3 - Effects of	i pentox	iryiine v	vs. cor	itrol trea	atment o	n ser	cum (creat	inine	
udv or Subarous	Pento Ioan Ima/di 1	SD Imakel 1	Total M	other Lithing and an	SD (madel 1	Total	Mainte		mean Difference	Mean Difference
<u>auy or subgroup N</u>	nean [mg/aL] ດອ	ວມ (mg/dL) 4 ກ		ean [mg/aL] 4 o	ວມ [mg/dL]		o 4 or	IV, FG	0 70 L0 27 4 77	iv, random, 95% Ci [mg/dL]
nnoja 2003 . L: 2010	2.0	1.2		1.9	U.8	1	0.1%			
n-i el 7017	2	1.12	16	2.24	1.18	16	0.2%		-0.24 [-1.04, 0.56]	
	1.32	0.47	30	1.19	0.44	15	1.7%		0.13 [-0.15, 0.41]	— —
avarro 2003			14	2.7	0.2	10	3.2%		0.10 [-0.10, 0.30]	- -
avarro 2003 avarro 1999	2.8	U.3	1 4			4.0	5.1%		-0.05 [-0.21, 0.11]	+
avarro 2003 avarro 1999 minorroava 2005	2.8 1	U.3 0.3	20	1.05	0.2	19				
avarro 2003 avarro 1999 ninorroaya 2005 aozheb 2010	2.8 1 1 03	0.3 0.3 0 2	20 35	1.05 n aa	0.2 0.236	। ७ २६	8 7 %		<u>በበ4 [በበዓ በ 17]</u>	_
avarro 2003 avarro 1999 ninorroaya 2005 oozbeh 2010 adriguez Moren 2006	2.8 1 1.03	0.3 0.3 0.3	20 35 20	1.05 0.99	0.2 0.235	19 35 40	8.2% 0.20		0.04 [-0.09, 0.17]	
avarro 2003 avarro 1999 ninorroaya 2005 oozbeh 2010 odriguez-Moran 2006	2.8 1 1.03 0.8	0.3 0.3 0.3 0.2	20 35 20	1.05 0.99 0.9	0.2 0.235 0.2	19 35 19	8.2% 8.2%		0.04 [-0.09, 0.17] -0.10 [-0.23, 0.03]	
avarro 2003 avarro 1999 ninorroaya 2005 oozbeh 2010 odriguez-Moran 2006 norbani 2012	2.8 1 1.03 0.8 1.15	0.3 0.3 0.3 0.2 0.25	20 35 20 44	1.05 0.99 0.9 1.19	0.2 0.235 0.2 0.3	19 35 19 50	8.2% 8.2% 10.5%		0.04 [-0.09, 0.17] -0.10 [-0.23, 0.03] -0.04 [-0.15, 0.07]	
avarro 2003 avarro 1999 ninorroaya 2005 oozbeh 2010 odriguez-Moran 2006 norbani 2012 armankaya 2003	2.8 1 1.03 0.8 1.15 1	0.3 0.3 0.2 0.25 0.2	20 35 20 44 25	1.05 0.99 0.9 1.19 1	0.2 0.235 0.2 0.3 0.2	19 35 19 50 25	8.2% 8.2% 10.5% 10.6%		0.04 [-0.09, 0.17] -0.10 [-0.23, 0.03] -0.04 [-0.15, 0.07] 0.00 [-0.11, 0.11]	
avarro 2003 avarro 1999 ninorroaya 2005 oozbeh 2010 odriguez-Moran 2006 norbani 2012 armankaya 2003 odriguez-Moran 2005	2.8 1 1.03 0.8 1.15 1 1.1	0.3 0.3 0.2 0.25 0.2 0.2 0.3	20 35 20 44 25 62	1.05 0.99 0.9 1.19 1.1	0.2 0.235 0.2 0.3 0.2 0.2	19 35 19 50 25 61	8.2% 8.2% 10.5% 10.6% 16.1%		0.04 [-0.09, 0.17] -0.10 [-0.23, 0.03] -0.04 [-0.15, 0.07] 0.00 [-0.11, 0.11] 0.00 [-0.09, 0.09]	
avarro 2003 avarro 1999 ninorroaya 2005 pozbeh 2010 pdriguez-Moran 2006 norbani 2012 armankaya 2003 pdriguez-Moran 2005 ing 1999	2.8 1 1.03 0.8 1.15 1 1.1 0.9	0.3 0.3 0.2 0.25 0.2 0.2 0.3 0.3	20 35 20 44 25 62 38	1.05 0.99 0.9 1.19 1 1.1 1.1	0.2 0.235 0.2 0.3 0.2 0.2 0.2	19 35 19 50 25 61 39	8.2% 8.2% 10.5% 10.6% 16.1% 16.3%		0.04 [-0.09, 0.17] -0.10 [-0.23, 0.03] -0.04 [-0.15, 0.07] 0.00 [-0.11, 0.11] 0.00 [-0.09, 0.09] -0.10 [-0.19, -0.01]	
avarro 2003 avarro 1999 ninorroaya 2005 oozbeh 2010 odriguez-Moran 2006 orbani 2012 armankaya 2003 odriguez-Moran 2005 ng 1999 avarro 2005	2.8 1 1.03 0.8 1.15 1 1.1 0.9 1	0.3 0.3 0.2 0.25 0.2 0.3 0.3 0.2 0.18	20 35 20 44 25 62 38 30	1.05 0.99 0.9 1.19 1 1.1 1.03	0.2 0.235 0.2 0.3 0.2 0.2 0.2 0.2	19 35 19 50 25 61 39 31	8.2% 8.2% 10.5% 10.6% 16.1% 16.3% 19.8%		0.04 [-0.09, 0.17] -0.10 [-0.23, 0.03] -0.04 [-0.15, 0.07] 0.00 [-0.11, 0.11] 0.00 [-0.09, 0.09] -0.10 [-0.19, -0.01] -0.03 [-0.11, 0.05]	
ivarro 2003 ivarro 1999 inorroaya 2005 iozbeh 2010 idriguez-Moran 2006 orbani 2012 rmankaya 2003 driguez-Moran 2005 ng 1999 varro 2005	2.8 1 1.03 0.8 1.15 1 1.1 0.9 1	0.3 0.3 0.2 0.25 0.2 0.3 0.2 0.18	20 35 20 44 25 62 38 30	1.05 0.99 0.9 1.19 1 1.1 1.03	0.2 0.235 0.2 0.3 0.2 0.2 0.2 0.14	35 19 50 25 61 39 31	8.2% 8.2% 10.5% 10.6% 16.1% 16.3% 19.8%		0.04 [-0.09, 0.17] -0.10 [-0.23, 0.03] -0.04 [-0.15, 0.07] 0.00 [-0.11, 0.11] 0.00 [-0.09, 0.09] -0.10 [-0.19, -0.01] -0.03 [-0.11, 0.05]	
varro 2003 varro 1999 ninorroaya 2005 ozbeh 2010 driguez-Moran 2006 orbani 2012 rmankaya 2003 driguez-Moran 2005 ng 1999 varro 2005	2.8 1 1.03 0.8 1.15 1 1.1 0.9 1	0.3 0.3 0.2 0.25 0.2 0.3 0.2 0.18	20 35 20 44 25 62 38 30 341	1.05 0.99 0.9 1.19 1.1 1.1 1.03	0.2 0.235 0.2 0.3 0.2 0.2 0.2 0.14	35 19 50 25 61 39 31 327	8.2% 8.2% 10.5% 10.6% 16.1% 16.3% 19.8%		0.04 [-0.09, 0.17] -0.10 [-0.23, 0.03] -0.04 [-0.15, 0.07] 0.00 [-0.11, 0.11] 0.00 [-0.09, 0.09] -0.10 [-0.19, -0.01] -0.03 [-0.11, 0.05] -0.03 [-0.06, 0.01]	

Cochrane CENTRAL, Ovid-MEDLINE and PubMed databases were searched for English-language articles without time or follow-up restriction. We included any randomized controlled trial (RCT) and quasi-RCT providing information on the effects of PTX on renal endpoints in patients with CKD. Outcomes of interest were change in renal function (GFR and/or serum creatinine), proteinuria and albuminuria and adverse effects to PTX treatment.

RESULTS

From a pool of 289 articles retrieved, we found 26 studies (1518 subjects) matching our search criteria. Among these, 24 studies were focused on diabetic patients while 2 were conducted on non-diabetic CKD population. There was high heterogeneity among studies with respect to sample size, CKD stage, dose of PTX employed, severity of proteinuria, type of comparator (e.g. placebo, standard therapy or RAS blockers). Information on the effects of PTX on hard renal outcomes (doubling of serum creatinine or need for chronic dialysis) were lacking in all the reviewed trials. PTX was effective in reducing proteinuria compared to control (MD -0.33 g/24h; 95% CI -0.54 to -0.13), a benefit that was more evident in patients with type-1 diabetes mellitus, higher proteinuria at baseline and early renal impairment. A slight improvement in renal function (MD 5.10 mL/min; 95% CI 2.53 to 7.67) was observed particularly in patients with more advanced CKD stage and in studies with longer follow-up. Conversely, cumulative analyses did not reveal any evident reduction in urinary albumin excretion, even in diabetic patients. The use of PTX was relatively safe as most trials recorded only minor gastrointestinal adverse effects.

Fig.4 – Effects of pentoxifylline vs. control treatment on eGFR/creatinine clearance

	Pento	xifylline		other	treatment			Mean Difference	Mean Difference
Study or Subgroup	Mean [mL/min]	SD [mL/min]	Total	Mean [mL/min]	SD [mL/min]	Total	Weight	IV, Random, 95% CI [mL/min]	IV, Random, 95% CI [mL/min]
Aminorroaya 2005	78.8	21.1	20	73.8	16.6	19	1.2%	5.00 [-6.88, 16.88]	
Badri 2013	73.9	31.7	12	83	22.2	6	0.3%	-9.10 [-34.34, 16.14]	← →
Ghorbani 2012	88.68	18.9	44	83.88	22.2	50	2.5%	4.80 [-3.51, 13.11]	
Goicoechea 2012	44.8	11.2	46	34.9	14.2	45	5.9%	9.90 [4.64, 15.16]	
Guerrero-Romero IDDM-MA 1995	102	27	10	100	24	8	0.3%	2.00 [-21.59, 25.59]	← →
Guerrero-Romero IDDM-PROT 1995	100	39	13	99	41	10	0.2%	1.00 [-32.09, 34.09]	← →
Guerrero-Romero NIDDM-MA 1995	88	26	12	100	19	11	0.5%	-12.00 [-30.51, 6.51]	←
Guerrero-Romero NIDDM-PROT 1995	90	18	12	91	29	10	0.4%	-1.00 [-21.66, 19.66]	← →
Jin-Lei 2012	57.7	29	16	48.2	30.2	16	0.4%	9.50 [-11.02, 30.02]	
Lin 2008	40.4	3.1	29	36.5	2.8	27	39.8%	3.90 [2.35, 5.45]	
Navarro 1999	24	5	14	23	3	10	14.2%	1.00 [-2.21, 4.21]	
Oliaei 2011	80.62	22.84	28	79.36	19.92	28	1.4%	1.26 [-9.97, 12.49]	
Perkins 2009	28.6	11.6	17	27.2	12.9	16	2.4%	1.40 [-6.99, 9.79]	
PREDIAN 2015	35.3	12	82	31.5	11.4	87	12.1%	3.80 [0.27, 7.33]	
Roozbeh 2010	103.57	9.69	35	102.82	7.88	35	9.1%	0.75 [-3.39, 4.89]	
Solerte 1987	109	12	10	98.1	10	11	1.9%	10.90 [1.40, 20.40]	│→
Zhang 2001	88.8	19.2	66	85.8	0.34	40	7.5%	3.00 [-1.63, 7.63]	
Total (95% CI)			466			429	100.0 %	3.42 [2.10, 4.75]	•
Heterogeneity: Tau ² = 0.52; Chi ² = 17.12	, df = 16 (P = 0.38)	; I² = 7%							
Test for overall effect: Z = 5.07 (P < 0.000	001)								Eavours (control) Eavours (Pentovifylline)

Fig.5 – Effects of pentoxifylline vs. control treatment on gastrointestinal intolerance

	Pentoxify	ylline	other treat	ment		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Roozbeh 2010	1	37	0	37	3.5%	3.00 [0.13, 71.34]	
Leyva-Jimenez 2009	1	10	0	10	3.6%	3.00 [0.14, 65.90]	
Zang 1999	2	38	0	39	3.9%	5.13 [0.25, 103.43]	
Guerrero-Romero IDDM-MA 1995	3	47	0	39	4.0%	5.83 [0.31, 109.61]	
Navarro 2005	3	30	0	31	4.1%	7.23 [0.39, 134.21]	
Ghorbani 2012	4	50	0	50	4.1%	9.00 [0.50, 162.89]	
Goicoechea 2012	8	46	0	45	4.4%	16.64 [0.99, 279.99]	_
Renke 2010	5	11	0	11	4.5%	11.00 [0.68, 177.72]	
Badri 2013	1	47	1	39	4.6%	0.83 [0.05, 12.84]	
PREDIAN 2015	18	82	9	87	63.3%	2.12 [1.01, 4.45]	
Total (95% CI)		398		388	100.0%	2.95 [1.64, 5.32]	-
Total events	46		10				
Heterogeneity: Tau ² = 0.00; Chi ² = 5	5.61, df = 9	(P = 0.7)	8); I² = 0%				
Test for overall effect: $Z = 3.60$ (P = 0.0003)							U.UU5 U.1 1 1U 2UU Eavoure [Poptovifulling]] Eavoure [control]
·	-						ravours (rentoxnynnier) ravours (control)

CONCLUSIONS

Although these findings point at some renoprotective effects of PTX, there is no conclusive evidence proving the usefulness of this agent for retarding end-stage kidney disease in subjects with CKD of various etiology. Future trials adequately powered and designed on hard clinical end-points are needed.

