İSKEMİK İNMELERDE GELECEKTE BİZİ NELER BEKLİYOR?

Uzm. Dr. Ali GÜR

Van Acil Sağlık Hizmetleri Başkanı

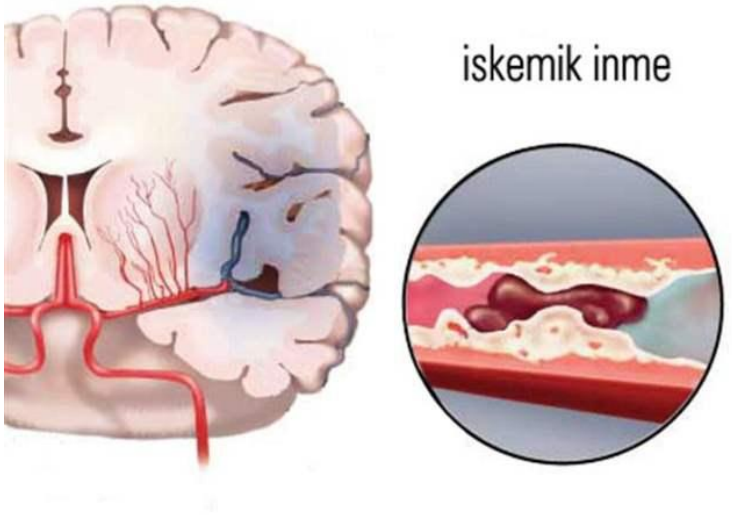
SUNUM PLANI

- Tanım ve İnmenin Önemi
- Güncel Tedavi Yaklaşımları
- Son Yayınlar

İnme

- Genellikle bir kan damarının yırtılması ya da pıhtı ile tıkanması sonucunda beyine kan akımının kesilmesi ya da azalmasıdır

- Acil bir durumdur.



İnme

- Dünya'da %85 iskemik, %15 hemorajik
- Ortak yolak değişmiş nöronal hipoperfüzyon
- Nöronlar serbest kan akımının değişikliğine son derece duyarlı ve perfüzyon kesilirse hızlıca ölürler
- Bu durum hızlı perfüzyon stratejilerinin amacını açıklamaktadır

Acil inme bakımı 4 basamaklı zincire bağımlıdır

İnmeden şüphelenilen hasta

1 TOPLUM

- İnme semptomlarının tanınması
- Uygun tepkinin verilmesi

2 ACİL ÇAĞRI SERVİSİ

- İnme belirtilerinin saptanması
- Acil hizmete yönlendirme önceliği

3 ACİL NAKİL (AMBULANS) HİZMETİ

- Hızla değerlendirme ve stabilize etme
- İnme merkezlerine transfer önceliği
- Hastanenin önceden bilgilendirilmesi

4 İNME ÜNİTESİ

- Hızla triyaj, değerlendirme ve görüntüleme
- Multidisipliner inme ekibi
- Doğru tanı
- Uygun tedavi

Öncelikli nakil ve tedavi

İNME

- Fibrinolitik tedaviye aday hastalar için hastane öncesi inme skalaları geliştirilmiştir.
  - Cincinati
  - Los Angeles
- Acil Serviste İnme Yönetimi (<3-4,5 Saat)

GÜNCEL TEDAVİ YAKLAŞIMLARI

- 1996 yılına kadar inmede bekle ve gör
- 1996 yılında akut iskemik inmede rtPA uygulandı.
- 1996-2010 yılları arasında ilk 3 saat
- 2010 yılından sonra ilk 4,5 saat
- 2018 yılında 24 saate kadar trombektomi

2019 yılından sonra….

Son Yayınlar

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Ther Adv Neurol Disord. 2019 Jan 20;12:1756286418821918. doi: 10.1177/1756286418821918. eCollection 2019.

Human tissue kallikrein in the treatment of acute ischemic stroke.

Alexander-Curtis M[1], Pauls R[2], Chao J[3], Volpi JJ[4], Bath PM[5], Verdoorn TA[2].

Author information

Abstract

Acute ischemic stroke (AIS) remains a major cause of death and disability throughout the world. The most severe form of stroke results from large vessel occlusion of the major branches of the Circle of Willis. The treatment strategies currently available in western countries for large vessel occlusion involve rapid restoration of blood flow through removal of the offending blood clot using mechanical or pharmacological means (e.g. tissue plasma activator; tPA). This review assesses prospects for a novel pharmacological approach to enhance the availability of the natural enzyme tissue kallikrein (KLK1), an important regulator of local blood flow. KLK1 is responsible for the generation of kinins (bradykinin and kallidin), which promote local vasodilation and long-term vascularization. Moreover, KLK1 has been used clinically as a direct treatment for multiple diseases associated with impaired local blood flow including AIS. A form of human KLK1 isolated from human urine is approved in the People's Republic of China for subacute treatment of AIS. Here we review the rationale for using KLK1 as an additional pharmacological treatment for AIS by providing the biochemical mechanism as well as the human clinical data that support this approach.

KEYWORDS: acute ischemic stroke; bradykinin; human tissue kallikrein; recombinant KLK1; vasodilation

Akut İskemik İnme tedavisinde İnsan Doku Kalliklerini

- Yeni bir farmakolojik yaklaşım için yerel kan akışının düzenleyicisi olan doğal enzim dokusu kallikrein (KLK1) kullanılabilirliğini artırmak
- Akut iskemik inmeli hastalarda KLK1 tedavisi ile mekanik tedavi, inme de klinik öncesi ve sonrası tedaviyi iyileştirmek..
- KLK1 ⟶ vazodilatasyon
- Düşük kalliklerin---- vazokonstriksiyon

Akut İskemik İnme tedavisinde İnsan Doku Kalliklerini

- Farelere IV KLK1 infüzyonu 24 saatlik süre içinde

↓

Beyin ödeminin azalması, hücrelerin apopitozdan korunması, anjiogenezis

- KLK1 İskemi ve reperfüzyon nedeni olduğu beyin hasarı bakımından kritik rol oynar
- inme sonrası hastalara ve plasebo grubuna 21 gün, günde 30 dk inf. (China)
- 90 gün sonra Europen Stroke Scale skorunda anlamlı fark tespit edilmiş.
- Yan etki %0,5-5. hipotansiyon, kusma,

Table 1. Summary of uKLK1 clinical trials since 2010.

Study	Reference	Design	Total *N*	Functional endpoint	Effect size[a]	Significance between groups
1	Wang and colleagues[91]	Prospective randomized double blind	44	NIHSS, 6–72 h post treatment	0.011	0.858
				NIHSS, 14 days post treatment	−0.04	$p = 0.049$
				MBI, 30 days post treatment	0.1	$p = 0.032$
2	Song and colleagues[92]	Prospective randomized controlled	27	NIHSS, 6 mo. after treatment	1.40	$p < 0.05$
				BI, 6 mo. after treatment	1.45	$p < 0.05$
3	Chen and colleagues[93]	Controlled	127	NHISS after treatment	1.09	$p < 0.05$
				BI, after treatment	2.85	$p < 0.05$
4	Meng and colleagues[94]	Controlled	120	NDS	1.00	$p < 0.05$
5	Wang and colleagues[95]	Controlled	200	NIHSS, 7 days after treatment	2.70	$p = 0.045$
				NISSS, 90 days after treatment	0.47	$p = 0.041$
				BI, 90 days after treatment	0.98	$p = 0.012$
6	Li and colleagues[96]	Randomized controlled	110	NIHSS, after treatment	0.41	$p = 0.04$
7	Miao and colleagues[97]	Nonrandomized controlled	30	Change in NIHSS	0.85	$p = 0.04$

[a]Effect size calculated by Cohen's *d* statistic for differences between treatment and control group for each endpoint. Significance between groups was the *p* value reported in the cited paper.

Akut İskemik İnme tedavisinde İnsan Doku Kalliklerini

- KLK1 tedavisi AIS tedavisinde iyileşmeye katkı sağlayıp patogenezinde rol oynayan nedenleri de önleyebilir.

Front Neurol. 2019 Jan 9;9:1119. doi: 10.3389/fneur.2018.01119. eCollection 2018.

Role of Decompressive Craniectomy in Ischemic Stroke.

Pallesen LP[1], Barlinn K[1], Puetz V[1].

Author information

Abstract

Ischemic stroke is one of the leading causes for death and disability worldwide. In patients with large space-occupying infarction, the subsequent edema complicated by transtentorial herniation poses a lethal threat. Especially in patients with malignant middle cerebral artery infarction, brain swelling secondary to the vessel occlusion is associated with high mortality. By decompressive craniectomy, a significant proportion of the skull is surgically removed, allowing the ischemic tissue to shift through the surgical defect rather than to the unaffected regions of the brain, thus avoiding secondary damage due to increased intracranial pressure. Several studies have shown that decompressive craniectomy reduces the mortality rate in patients with malignant cerebral artery infarction. However, this is done for the cost of a higher proportion of patients who survive with severe disability. In this review, we will describe the clinical and radiological features of malignant middle cerebral artery infarction and the role of decompressive craniectomy and additional therapies in this condition. We will also discuss large cerebellar stroke and the possibilities of suboccipital craniectomy.

KEYWORDS: craniectomy; middle cerebral artery infarction; posterior circulation stroke; prognosis; stroke

İskemik İnmede Decompresive Craniectomy'nin Rolü

- Randomize–kontrollü bir meta analiz çalışması
- Geniş enfarklı hastalarda ödemin komlikasyon ile transtentorial herniasyon ve ölümcül sonuç
- Özellikle orta serebral arterin oklüzyonu yüksek mortalite

İskemik İnmede Decompresive Craniectomy'nin Rolü

- Craniektomi ile etkilenen alandaki basınç artışı azaltılıp etkilenmeyen alana doğru herniasyon ve daha fazla dokunun etkilenmesi önleniyor
- Orta serebral arter enfartının dekompresyonla iyileşmesi
- Dekompresif cerrahinin <60 yaş altında (%19 vs. 4%)
- Çok geniş MCA enfarklarında tek yol..

TABLE 2 | Overview of the randomized controlled trials (RCTs).

Study name	Age (years)	Inclusion from symptom onset (hours)	Imaging criteria	Clinical criteria	Primary outcome parameter	Main finding	Patients included, n (DC/BMT)
DECIMAL	18–55	<24	>50% ischemic MCA territory; MRI-DWI infarct volume >145 cc	NIHSS >15; NIHSS 1a ≥1	mRS 0–3 at 6 months	52.5% absolute mortality reduction with DC compared to BMT ($p < 0.0001$); no significant difference between DC and BMT regarding mRS 0–3	38 (20/18)
DESTINY I	18–60	>12 to <36	≥2/3 MCA territory with basal ganglia; with/without ACA/PCA territory	NIHSS >18 (non-dominant) or >20 (dominant); NIHSS 1a ≥1	Sequential design: mortality after 30 days; mRS 0–3 vs. 4–6 at 6 months	Mortality reduction from 88% to 47% with DC after 30 days ($p = 0.02$)	32 (17/15)
HAMLET	18–60	<96	≥2/3 MCA territory; formation of space occupying edema	NIHSS ≥16 (right) or ≥21 (left); NIHSS 1a ≥1; GCS <13 (right-sided) or GCS (eye and motor score) < 9 (left-sided)	mRS 0–3 vs. 4–6 at 12 months	DC with no effect on primary outcome measure but significant reduction of case fatality (ARR 38%)	64 (32/32)
Zhao et al.	18–80	<48	≥2/3 MCA territory; with/without ACA/PCA territory; space-occupying edema	GCS (eye and motor score) ≤9	mRS 0–4 vs. 5–6 at 6 months	Reduction of mortality (DC 12.5% vs. BMT 60.9 %, $p = 0.001$) and mRS 5–6 (DC 33.3% vs. BMT 82.6 %, $p = 0.001$)	47 (24/23)
HeADDFIRST	18–75	<96	≥50% ischemic MCA territory(<5h) or complete MCA infarction (<48h)	NIHSS ≥18; NIHSS 1a <2	survival 21 days	Non-significant reduction of mortality at 21 days (DC 21% vs. BMT 40%, $p = 0.39$)	24 (14/10)
DESTINY II	>60	<48	≥2/3 MCA territory with basal ganglia	NIHSS >14 (non-dominant) or >19 (dominant), reduced level of consouscness on NIHSS	mRS 0–4 at 6 months	Significant reduction of severe disability (mRS scores 5–6: DC 38% vs. BMT 18%, $p = 0.04$)	112 (49/63)
Slezins et al.	>18	<48	≥2/3 MCA; with/without ACA/PCA territory or cerebral infarct volume >145 cc	NIHSS >15	mRS 0–4 vs. 5–6 at 12 months	Significant mortality reduction (DC 45.5% vs. BMT 7.7%, $p = 0.03$)	24 (11/13)
HeMMI	18–65	≤72	≥2/3 MCA territory; with/without ACA/PCA territory	GCS 6–14 (right-side) or 5–9 (left-side); GCS 15 and NIHSS ≥1a	mRS 0–3 vs. 4–6 at 6 months	No significant differences (DC 23.1% vs. BMT 38.4%, $p = 0.476$)	29 (16/13)

ACA, indicates anterior cerebral artery; ARR, absolute risk reduction; BMT, best medical treatment; DC, decompressive craniectomy; GCS, Glasgow Coma Scale; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PCA, posterior cerebral artery.

NE ZAMAN cerrahi?

Front Neurol. 2019 Jan 25;10:11. doi: 10.3389/fneur.2019.00011. eCollection 2019.

Timing of Decompressive Craniectomy for Ischemic Stroke and Traumatic Brain Injury: A Review.

Shah A[1], Almenawer S[2], Hawryluk G[1].

Author information

Abstract

While studies have demonstrated that decompressive craniectomy after stroke or TBI improves mortality, there is much controversy regarding when decompressive craniectomy is optimally performed. The goal of this paper is to synthesize the data regarding timing of craniectomy for malignant stroke and traumatic brain injury (TBI) based on studied time windows and clinical correlates of herniation. In stroke patients, evidence supports that early decompression performed within 24 h or before clinical signs of herniation may improve overall mortality and functional outcomes. In adult TBI patients, published results demonstrate that early decompressive craniectomy within 24 h of injury may reduce mortality and improve functional outcomes when compared to late decompressive craniectomy. In contrast to the stroke data, preliminary TBI data have demonstrated that decompressive craniectomy after radiographic signs of herniation may still lead to improved functional outcomes compared to medical management. In pediatric TBI patients, there is also evidence for better functional outcomes when treated with decompressive craniectomy, regardless of timing. More high quality data are needed, particularly that which incorporates a broader set of metrics into decision-making surrounding cranial decompression. In particular, advanced neuromonitoring and imaging technologies may be useful adjuncts in determining the optimal time for decompression in appropriate patients.

KEYWORDS: TBI; decompressive hemicraniectomy; herniation; stroke; timing

PMID: 30740085 PMCID: PMC6355668 DOI: 10.3389/fneur.2019.00011

TABLE 1 | Decompressive craniectomy for stroke studies.

	Author	Study design	Patients	Selection criteria	Treatment	Total no of patients	Time to DC	Mortality *n*(%)	Functional outcome at 6 months	Functional outcome at 12 months	Conclusions
Stroke	Vahedi et al. (8)	Randomized controlled trial	Adult patients with MCA infarction	Patient age 18–55 years, within 24 h of a malignant MCA infarction, NIHSS ≥ 16,; >50% of the MCA territory involved on CT; DWI infarct volume >145 cm^3	DC	20	Avg 20.5 ± 8.3 h (range, 7–43 h)	5 (25)	mRS score ≤3: 25%	mRS score ≤3: 50%	When compared to medical management, the DC group demonstrated an increase in the number of patients with moderate disability by more than half and demonstrated a reduction in the mortality rate by more than half.
					Medical management	18	NA	14 (78)	mRS score ≤3: 5.6%	mRS score ≤3: 22.2%	
	Juttler et al. (9)	Randomized controlled trial	Adult patients with MCA infarction	Patient age 18–60 years, at least 2/3 of MCA territory infarction with basal ganglia involvement, NIHSS >18 for non-dominant hemisphere, NIHSS > 16 for dominant hemisphere, symptoms > 12 h but <36 h before possible DC	DC	17	Within 36 h after stroke	2 (11.8)	mRS score ≤3: 47%	mRS score ≤3: 47%	DC reduces mortality in large hemispheric stroke. Functional outcomes at 6 and 12 months were comparable between both groups
					Medical management	15	NA	8 (53.3)	mRS score ≤3: 27%	mRS score ≤3: 27%	
	Hofmeijer et al. (10)	Randomized controlled trial	Adult patients with MCA infarction	Patient age 18–60, at least 2/3 of MCA territory stroke within 96 h of treatment, NIHSS score >16 right sided lesions or >21 left sided lesions,	DC	32	Within 96 h after stroke	7 (22)	NA	mRS score ≤3:25%	DC can improve fatality and functional outcomes when performed within 48 h; however, when delayed up to 96 h, there was no improvement in functional outcomes.
					Medical management	32		19(59)	NA	mRS score ≤3:25%	
	Vibbert et al. (3)	Randomized controlled trial	Adult patients with MCA infarction	Patient age 18–60, at least 2/3 of MCA territory stroke within 96 h of treatment, NIHSS score >16 right sided lesions or >21 left sided lesions,	DC	32	Within 96 h after stroke	NA	NA	mRS score ≤3:25%	DC can improve fatality (absolute risk reduction of 38%); however, there was no improvement in functional outcomes.
					Medical management	32		NA	NA	mRS score ≤3:25%	
	Schwab et al. (12)	Prospective cohort	Adult patients with MCA infarction	Patients younger than 70, >50% MCA territory infarction noted on CT imaging	Early DC	31	Within 24 h after stroke	5 (16)	Avg Barthel Index Score: 68.8	NA	Earlier DC was associated with lower mortality. There was a trend toward better functional outcomes, and the patients spent less time in the ICU

(Continued)

TABLE 1 | Continued

Author	Study design	Patients	Selection criteria	Treatment	Total no of patients	Time to DC	Mortality *n*(%)	Functional outcome at 6 months	Functional outcome at 12 months	Conclusions
				Late DC	32	>24 h after stroke	11 (34.4)	Avg Barthel Index Score: 62.6	NA	
				Medical management	55		43 (78)	Avg Barthel Index Score: 60	NA	
Wang et al. (13)	Retrospective cohort	Adult patients with MCA infarction	Patients with 1st stroke >90% MCA infarction	Early DC	11	Within 24 h after stroke	3 (27)	Mean Glasgow Outcome Score: 2.5	NA	While the mortality rates were comparable between groups, severe disability may be reduced in early treated patients
				Late DC	10	>24 h after stroke	3 (30)	Mean Glasgow Outcome Score: 2.45	NA	
				Medical management	41		9 (22)	Mean Glasgow Outcome Score: 2.73	NA	
Cho et al. (14)	Retrospective cohort	Adult patients with MCA infarction	Patients with > 50% MCA infarction with NIHSS score > 20	Ultra-early DC	12	Within 6 h after stroke	1 (8.3)	Avg Barthel Index Score: 70	NA	DC before neurologic compromise may reduce the mortality rate and increase the conscious recovery rate
				Delayed DC	30	>6 h after stroke	11 (36.7)	Avg Barthel Index Score: 52.9	NA	
				Medical management	10		8 (80)	Avg Barthel Index Score: 55	NA	
Mori et al. (15)	Retrospective cohort	Adult patients with MCA infarction	Patients <85 years of age with patients with embolic hemispheric infarction volume > than 200 cm3	Early DC	21	DC before brain herniation	4 (19.1)	Avg Barthel Index Score: 52.9	NA	Early DC before the onset of brain herniation should be performed to improve mortality and functional recovery. DC after signs of herniation may be too late for functional benefit
				Late DC	29	DC after brain herniation	8 (27.6)	Avg Barthel Index Score: 26.9	NA	
				Medical management	21		15 (71.4)	Avg Barthel Index Score: 28.3	NA	
Elsawaf et al. (16)	Prospective cohort	Adult patients with MCA infarction	Patients with malignant MCA infarction	DC based on clinical status	27	DC with deterioration of consciousness	14 (52)	Mean mRS Score: 4.7	NA	Early prophylactic DC yields better clinical and radiographic outcomes than DC based on clinical status
				Early DC	19	DC within 6 h of stroke	2 (10.5)	Mean mRS Score: 3.5	NA	

Front Cell Dev Biol. 2019 Jan 8;6:175. doi: 10.3389/fcell.2018.00175. eCollection 2018.

Hypoxia Mimetic Agents for Ischemic Stroke.

Davis CK[1], Jain SA[2], Bae ON[3], Majid A[2], Rajanikant GK[1].

Author information

Abstract

Every year stroke claims more than 6 million lives worldwide. The majority of them are ischemic stroke. Small molecule-based therapeutics for ischemic stroke has attracted a lot of attention, but none has been shown to be clinically useful so far. Hypoxia-inducible factor-1 (HIF-1) plays a crucial role in the transcriptional adaptation of cells to hypoxia. Small molecule-based hypoxia-mimetic agents either stabilize HIF-1α *via* HIF-prolyl hydroxylases (PHDs) inhibition or through other mechanisms. In both the cases, these agents have been shown to confer ischemic neuroprotection *in vitro* and *in vivo*. The agents which act *via* PHD inhibition are mainly classified into iron chelators, iron competitors, and 2 oxoglutarate (2OG) analogs. This review discusses HIF structure and key players in the HIF-1 degradation pathway as well as the genes, proteins and chemical molecules that are connected to HIF-1 and how they affect cell survival following ischemic injury. Furthermore, this review gives a summary of studies that used PHD inhibitors and other HIF-1α stabilizers as hypoxia-mimetic agents for the treatment of ischemic injury.

KEYWORDS: hypoxia mimetic agent; hypoxia-inducible factor-1; iron chelators; ischemic stroke; neuroprotection

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İskemi İnme için Hipoksik mimetik Ajanlar

- Hipoksi, hücrenin çekirdekte HIF-1 biriktirmesine neden olur
- HIF prolyl hydroxylases (PHDs) spesifik HIF-1 hedefli genler yukarı doğru düzenleyerek hücrelerin olumsuz durumun üstesinden gelmesine yardımcı oluyor.
- Olaylar Gen Expresyonu yolu ile oluşmaktadır
- İn vivo ortamda çalışmaları yapılmış.

Özet

- Akut İskemik İnme tedavisinde İnsan Doku Kalliklerini rutin kullanıma girebilir..
- İskemik İnmede Dekompresif Craniektomi işlemi yaygınlaşacak…
- Hipoksik mimetik ajanlar belkide tedavi amaçlı iskemik inmelerde kullanılacak…
- ……..???

TEŞEKKÜRLER…