효과적이고 안전한 관절통 치료

김 용 길
울산의대 서울아산병원 류마티스 내과

강의 내용

- 관절통을 호소하는 환자에게 적절한 치료제 선택은?
- NSAIDs의 위장관계 부작용을 줄이기 위한 방법은 무엇인가?
- NSAIDs의 심혈관계 부작용을 줄이기 위한 방법은 무엇인가?
- 심혈관 및 위장관계 부작용을 줄이기 위한 NSAIDs 사용의 권장사항

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증례 1

- 65세의 여자 환자.
  약 1년 전부터 시작된 양측 무릎 통증
  통증은 주로 비탈길이나 계단을 내려올 때 심함
  검진상 양측 무릎관절에서 염발음 촉지
  단순 방사선 사진상 내측 관절 간격이 좁아짐
  관절통을 완화하기 위한 약제 선택방법은?

근골격계 통증 완화제

- Acetaminophen
- NSAIDs
- Tramadol
- Narcotic analgesics

Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis

Bruno R da Costa*, Stephan Reichenbach*, Noah Keller, Linda Nartey, Simon Wandel, Peter Jüni, Sven Trelle

Summary

Background Non-steroidal anti-inflammatory drugs (NSAIDs) are the backbone of osteoarthritis pain management. We aimed to assess the effectiveness of different preparations and doses of NSAIDs on osteoarthritis pain in a network meta-analysis.

Methods For this network meta-analysis, we considered randomised trials comparing any of the following interventions: NSAIDs, paracetamol, or placebo, for the treatment of osteoarthritis pain. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the reference lists of relevant articles for trials published between Jan 1, 1980, and Feb 24, 2015, with at least 100 patients per group. The prespecified primary and secondary outcomes were pain and physical function, and were extracted in duplicate for up to seven timepoints after the start of treatment. We used an extension of multivariable Bayesian random effects models for mixed multiple treatment comparisons with a random effect at the level of trials. For the primary analysis, a random walk of first order was used to account for multiple follow-up outcome data within a trial. Preparations that used different total daily dose were considered separately in the analysis. To assess a potential dose-response relation, we used preparation-specific covariates assuming linearity on log relative dose.

Findings We identified 8973 manuscripts from our search, of which 74 randomised trials with a total of 58 556 patients were included in this analysis. 23 nodes concerning seven different NSAIDs or paracetamol with specific daily dose of administration or placebo were considered. All preparations, irrespective of dose, improved point estimates of pain symptoms when compared with placebo. For six interventions (diclofenac 150 mg/day, etoricoxib 30 mg/day, 60 mg/day, and 90 mg/day, and rofecoxib 25 mg/day and 50 mg/day), the probability that the difference to placebo is at or below a prespecified minimum clinically important effect for pain reduction (effect size [ES] −0·37) was at least 95%. Among maximally approved daily doses, diclofenac 150 mg/day (ES −0·57, 95% credibility interval [CrI] −0·69 to −0·46) and etoricoxib 60 mg/day (ES −0·58, −0·73 to −0·43) had the highest probability to be the best intervention, both with 100% probability to reach the minimum clinically important difference. Treatment effects increased as drug dose increased, but corresponding tests for a linear dose effect were significant only for celecoxib (p=0·030), diclofenac (p=0·031), and naproxen (p=0·026). We found no evidence that treatment effects varied over the duration of treatment. Model fit was good, and between-trial heterogeneity and inconsistency were low in all analyses. All trials were deemed to have a low risk of bias for blinding of patients. Effect estimates did not change in sensitivity analyses with two additional statistical models and accounting for methodological quality criteria in meta-regression analysis.

Interpretation On the basis of the available data, we see no role for single-agent paracetamol for the treatment of patients with osteoarthritis irrespective of dose. We provide sound evidence that diclofenac 150 mg/day is the most effective NSAID available at present, in terms of improving both pain and function. Nevertheless, in view of the safety profile of these drugs, physicians need to consider our results together with all known safety information when selecting the preparation and dose for individual patients.

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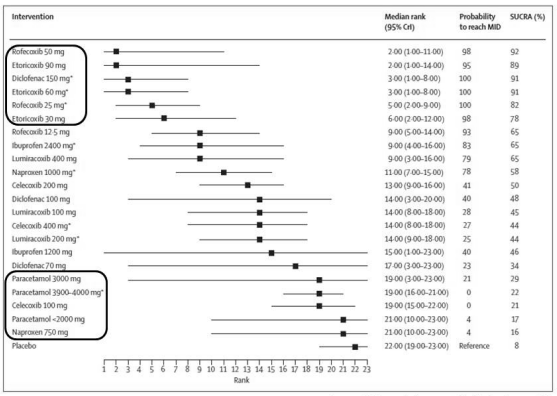
Treatment effect



Costa BR et al. Lancet 2016 (online published)

Acetaminophen ?

DG News

Top Stories This Week

Paracetamol Not Clinically Effective in Treating Osteoarthritis Pain or Improving Physical Function

NEW YORK -- March 18, 2016 -- In a large-scale analysis of pain-relief medication for osteoarthritis, researchers found that paracetamol does not meet the minimum standard of clinical effectiveness in reducing pain or improving physical function in patients with knee and hip osteoarthritis...

Comment | Rate

HIV-Positive Young Males Have Higher Rates of Bone Loss Than Females

LOS ANGELES -- March 10, 2016 -- Rates of low bone mass are greater in HIV-positive males than in females, according to a study published in the Journal of Acquired Immune Deficiency Syndromes, Grace Aldrovandi, MD, Division of Infectious Diseases, Children's Hospital Los Angeles, Los Angeles...

Comment | Rate

NSAID의 선택

- 환자가 지니고 있는 NSAIDs의 부작용에 대한 위험인자 여부에 의해 결정
- 의사가 처방에 익숙한 약제를 선택
- 일반적으로 한가지 약제를 약 2주간 사용한 후 효과가 적절하지 않으면 화학적 구조가 다른 종류의 NSAID로 교체하는 것이 권장

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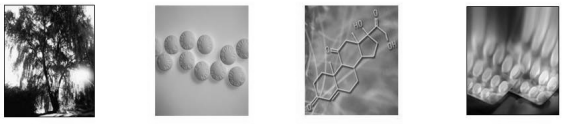
  관절통을 완화하기 위한 약제 선택방법은?

1. 증상이 심하지 않으면 Acetaminophen 부터 사용하여 본다.
2. NSAID 사용 시 부작용 위험인자여부를 따져본다.
3. 특별한 위험인자가 없다면 익숙한 약제를 사용한다.
4. 투약 2주 후 효과가 없다면 다른 NSAID로 바꿔본다.

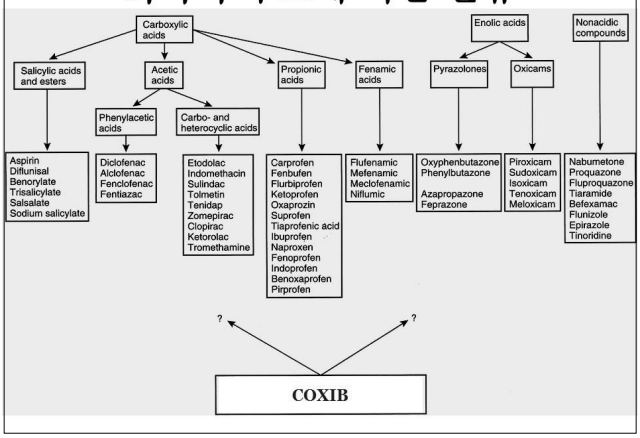
"History of NSAIDs"

Willow tree Late 1700s | Aspirin 1897 | Glucocorticoid (cortisone) 1949 | NSAIDs 1960s–1970s



Benedek TG. *Primer on the Rheumatic Diseases.* 11th ed. 1997:1–5; Benedek TG.

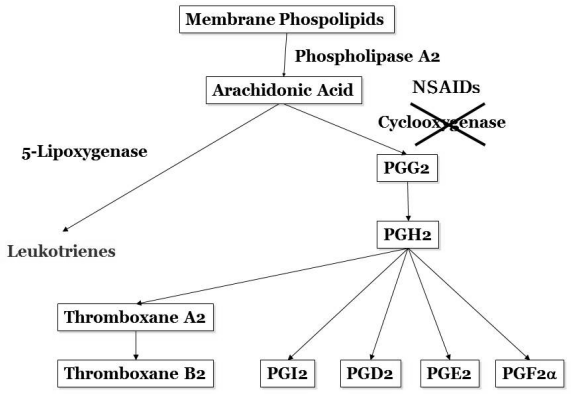
화학적 구조에 따른 분류



작용시간에 따른 분류

- **Short acting**
  - Aspirin
  - Diclofenac
  - Etodolac
  - Fenoprofen
  - Ibuprofen
  - Indomethacin
  - Ketoprofen
  - Mefenamic acid
- **Long acting**
  - Meloxicam
  - Nabumetone
  - Naproxen
  - Phenylbutazone
  - Piroxicam
  - Sulindac
  - Tenoxicam

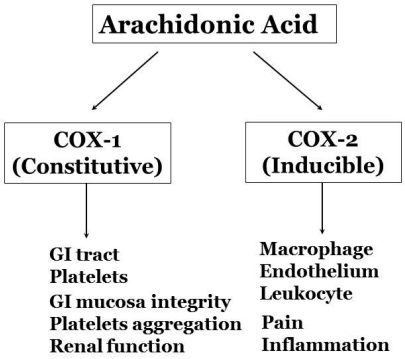
작용기전



부작용

Gastrointestinal	Indigestion, GERD, Erosions, Peptic ulcer, G-I bleeding and perforation
Cardiovascular	MI, Stroke
Hepatic	Liver enzyme elevation, Cholestasis
Hematologic	Thrombocytopenia, Leucopenia, Red cell aplasia Hemolytic anemia
Renal	Acute renal failure, Interstitial nephritis, Hyperkalemia, Hyponatremia,
Skin	Photosensitivity, Erythema multiforme, Urticaria, Toxic epidermal necrolysis
Respiratory	Bronchospasm, Eosinophilic pneumonitis
CNS	Headache, Dizziness, Personality change, Aseptic meningitis

Isotypes of cyclooxygenase



Conventional NSAIDs vs COX-2 inhibitors

	Conventional NSAIDs	COX-2 inhibitors
GI	Dyspepsia GI ulcer GI bleeding	Decreased GI ulcer & bleeding
CV	Platelet dysfunction	Arterial thrombosis Increased IHD risk (rofecoxib)

COX-1 vs. COX-2

COX-1 preferential	Equipotent for COX-1 and COX-2	COX-2 preferential	COX-2 selective
Indomethacin	Diclofenac	Meloxicam	Celecoxib
Naproxen		Nimesulide	Etoricoxib
Piroxicam		Etodolac	
Aspirin			
Ibuprofen			

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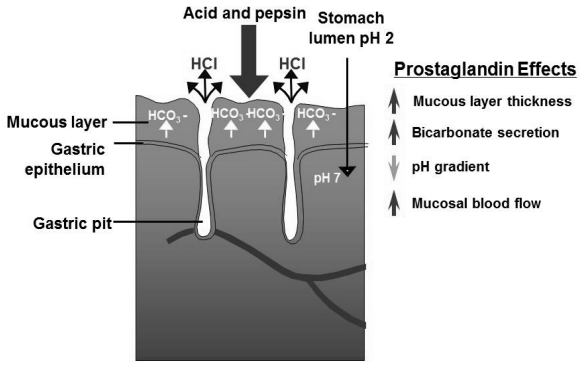
증례 2

- 42세 여자 환자
  5년 전 류마티스 관절염 진단
  1년 전 위궤양으로 치료받은 병력
  이 환자에서 적절한 NSAID는?

위점막 보호기전



NSAIDs의 위장관 부작용

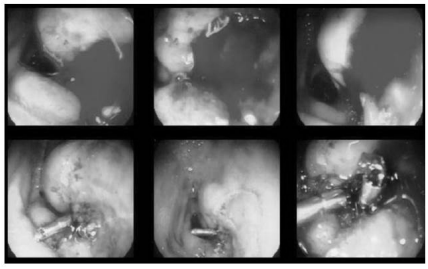
- 소화불량, 속쓰림 : 60%
- 내시경에서 위 또는 십이지장 궤양 : 20-30%
- 심각한 위장관 부작용(천공, 출혈) : 1-1.5%/year

상부위장관 부작용의 위험인자들

- Age ≥ 65
- History of peptic ulcer disease
- History of upper GI bleeding
- Comorbid medical conditions
- Oral glucocorticoids
- Anticoagulants
- Aspirin

Ulcerogenic effects of corticosteroids

- Gastrointestinal effects:
  1) GI ulcer disease (RR 2.0)
  2) co-treatment with NSAIDs (RR 4.4)



Clinical probability for significant ulcer complications

	RR vs. NSAIDs alone (literatures)	Base-case estimate (%/year)
NSAIDs alone	1.0	3
NSAIDs + ASA	2.5	7.5
NSAIDs + PPI	0.2 – 0.5	1.5
NSAIDs + ASA + PPI	Not identified	2.5
Coxib alone	0.5	1.5
Coxib + ASA	2.5	7.5

위장관 부작용을 줄이기 위한 전략들

- **비선택적 NSAID + 위장 보호약제**
  - PPI : 가장 이상적
  - H_2 blocker : 고용량이 필요, 보험 문제
  - Misoprostol : 설사와 복통이 흔함
- **선택적 COX-2 억제제 : celecoxib, etoricoxib**
  - Aspirin과 같이 투여할 경우 위장관 보호 효과 상실
- **H. pylori eradication**
  - 궤양이 있었던 고위험군의 환자에서
  - 궤양이 없더라도 장기간 NSAIDs 사용예정인 경우

COX-2 i + PPI vs. COX-2 i

Celecoxib + esomeprazol 20 mg bid vs. Celebrex
Patients with recent ulcer bleeding Hx

	Probability of recurrent bleeding		p*
	Combined-treatment group	Control group	
All patients	0% (0 to 0)	8·9 (4·1 to 13·7)	0·0004
Patients who did not take concomitant aspirin	0% (0 to 0)	7·1 (2·4 to 11·8)	0·004
Patients who took concomitant aspirin	0% (0 to 0)	19·0 (2·2 to 35·8)	0·03
Per-protocol analysis	0% (0 to 0)	6·0 (1·4 to 10·6)	0·01

Data are percentage (95% CI). *Calculated with the log-rank test. We used the Kaplan-Meier method because the probability of recurrent ulcer bleeding depended on the duration of treatment, which was assumed to be stable with time.

Table 2: Kaplan-Meier estimates of the likelihood of recurrent ulcer bleeding at 13 months

Chan FK et al. Lancet 2007;369:1621-26

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  이 환자에서 적절한 NSAID는?

1. 비선택적 NSAID + PPI
2. 비선택적 NSAID + misoprostol 20 ug bid-qid → 부작용 빈도
3. 비선택적 NSAID + Famotidine 40 mg bid → 보험 문제
4. 선택적 COX2 억제제 (+ PPI)

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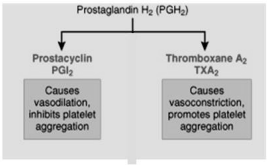
증례 3

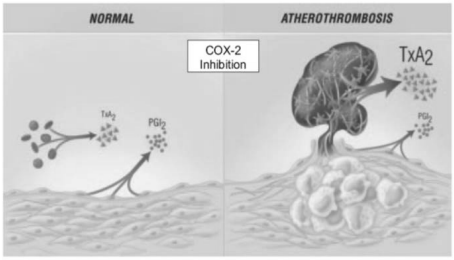
- 50세 남자 환자
  4년 전부터 발생한 요통
  2년 전 심근경색증으로 치료 받은 병력
  적절한 NSAID는?

NSAID의 심혈관계에 대한 영향

- **수축기 및 이완기 혈압의 상승 (약 5 mmHg)**
  → 심부전 또는 심근경색증의 위험도 증가
- **선택적 COX-2 억제제**
  - 혈관내피세포(COX-2 발현)의 prostacyclin 생성 감소
    혈소판(COX-1 발현)에서 TXA2 생성은 억제하지 않음

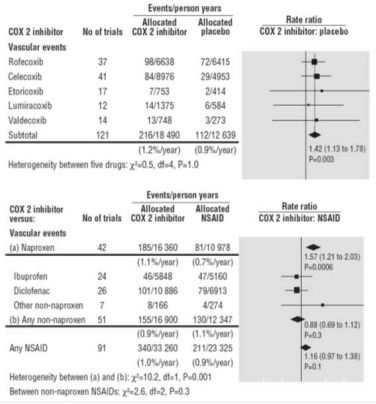


COX inhibition for PGI2 and TXA2 production



Antman EM et al. Circulation 2007;115:1634-42

CV risk : COX-2 inhibitor *vs.* traditional NSAIDs



COX 2 inhibitor	No of trials	Events/person years: Allocated COX 2 inhibitor	Events/person years: Allocated placebo
Vascular events			
Rofecoxib	37	98/6638	72/6415
Celecoxib	41	84/8976	29/4953
Etoricoxib	17	7/753	2/414
Lumiracoxib	12	14/1375	6/584
Valdecoxib	14	13/748	3/273
Subtotal	121	216/18 490	112/12 639
		(1.2%/year)	(0.9%/year)

Heterogeneity between five drugs: χ^2=0.5, df=4, P=1.0

COX 2 inhibitor versus:	No of trials	Events/person years: Allocated COX 2 inhibitor	Events/person years: Allocated NSAID
Vascular events			
(a) Naproxen	42	185/16 360	81/10 978
		(1.1%/year)	(0.7%/year)
Ibuprofen	24	46/5848	47/5160
Diclofenac	26	101/10 886	79/6913
Other non-naproxen	7	8/166	4/274
(b) Any non-naproxen	51	155/16 900	130/12 347
		(0.9%/year)	(1.1%/year)
Any NSAID	91	340/33 260	211/23 325
		(1.0%/year)	(0.9%/year)

Heterogeneity between (a) and (b): χ^2=10.2, df=1, P=0.001
Between non-naproxen NSAIDs: χ^2=2.6, df=2, P=0.3

Kearney PM et al. BMJ 2006; 332:1302

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Naproxen

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증례 4

- 40세 남자 환자
  8년 전 강직척추염 진단
  1년 전 위출혈 병력 및 협심증 치료 중
  적절한 NSAID 처방 전략은?

심혈관계 질환의 위험인자

- 허혈성 심질환
- 중풍
- 말초혈관 질환
- 10-year cardiovascular event risk (Framingham equation) ≥ 10%

10-year CVD risk calculator

(http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof.)

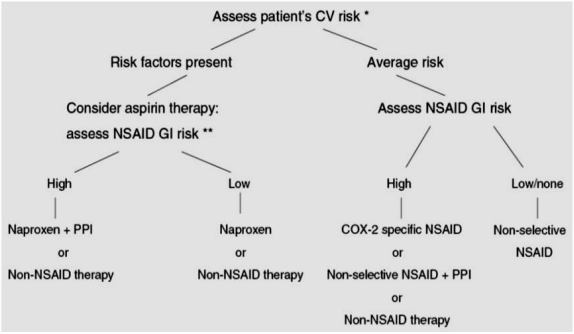
Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack

The risk assessment tool below uses information from the Framingham Heart Study to predict a person's chance of having a heart attack in the next 10 years. This tool is designed for adults aged 20 and older who do not have heart disease or diabetes. To find your risk score, enter your information in the calculator below.

Age:	years
Gender:	Female/Male
Total Cholesterol:	mg/dL
HDL Cholesterol:	mg/dL
Smoker:	No/Yes
Systolic Blood Pressure:	mm/Hg
Are you currently on any medication to treat high blood pressure.	No/Yes

→ **CVD risk score**

Decision tree for NSAID use



증례 4

- 40세 남자 환자
  8년 전 강직척추염 진단
  1년 전 위출혈 병력 및 협심증 치료 중
  적절한 NSAID 처방 전략은?

Naproxen + PPI

요약

- 심하지 않은 관절통은 단순 진통제부터 시작하는 것을 추천하며, 효과가 없거나 악화 시 NSAID 사용을 시도할 수 있다.
- NSAID 사용 시 2주 정도 효능 평가 후 유지 변경을 고려할 수 있다.
- NSAID 사용 시 위장관계 및 심혈관계 부작용의 우려가 가장 크다.
- 위장관계 부작용 위험이 있는 환자에서는 비선택적 NSAID+PPI 또는 선택적 COX2 억제제가 권장되며 COX2 억제제 + PPI가 가장 이상적이다.
- 대부분의 NSAID(COX-2 억제제)는 심혈관계 부작용을 증가시킬 우려가 있으므로 심혈관계 위험인자가 있는 환자에서는 Naproxen이 선호된다.
- 위장관계 및 심혈관계 위험인자가 모두 있는 경우 단순 진통제 혹은 Naproxen + PPI를 사용해 볼 수 있다.