Paracetamol or NSAID's in acute musculoskeletal syndromes

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON41695

Source
ToetsingOnline

Brief title
The PanAm Study

Condition

- Other condition
- Bone and joint injuries
- Tendon, ligament and cartilage disorders

Synonym
Strains and sprains

Health condition

traumatische musculoskeletale aandoeningen exclusief fracturen

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Acetaminophen, Analgesia, Non-Steroidal Anti-Inflammatory Drugs, Wounds and injuries

Outcome measures

Primary outcome

The primary outcome is decrease in pain, measured by differences in Numeric Rating Scales (NRS). A decrease of 1.3 in NRS is considered clinically relevant. This analgesic effectiveness will be monitored by repetitive measurements of pain scores using the NRS during the stay in the emergency department or during the visit to the general practitioner. After discharge, pain is measured and documented during three consecutive days in the home environment.

Secondary outcome

Secondary outcomes are occurrence of adverse events after use of pain medication.The safety profile of the different drugs involved will be investigated by monitoring the occurrence of adverse events in the emergency department or general practice and during a period of three days after discharge. Other secondary outcomes are patient satisfaction about pain relief, need for additional pain medication and cost-effectiveness of the different pain management strategies.

Special attention is given to the group of patients older then 60 years (block-randomization), as these patients have the highest risk of having

NSAID-related adverse events.

Study description

Background summary

In The Netherlands, each year approximately 3.1 million injuries are treated medically. This mainly consists of sports related (1.4 million) and private (1.2 million) injuries. Most of these injuries are musculoskeletal injuries, without a fracture, often called sprains, contusions or acute musculoskeletal syndromes. Patients with acute musculoskeletal injuries are distributed throughout the whole population.
They can have any age, sex or cultural background. They are frequently treated by a general practitioner or an emergency physician. Pain management is a crucial part of this treatment. Different drugs can be used for this purpose. Often used are paracetamol and Non-Steroidal Anti-Inflammatory Drugs (NSAID's). Which of the drugs (paracetamol or NSAID's) the treating physician prescribes, often depends on the experience and preference of the physician. To guide staff treating acute patients, in 2010 the Dutch Institute for Healthcare Improvement CBO published a guideline on treating pain in trauma patients. The authors of this guideline mention that there is a preference for paracetamol in treating pain in minor trauma and acute musculoskeletal syndromes. However, as also mentioned in the guideline, this is solely based on two studies with a low level of evidence. In order to fill up this gap in medical literature, there is need for confirmative evidence that paracetamol works as well as NSAID's in managing pain after acute musculoskeletal syndromes. By doing the current project, the research group aims to deliver a high level of evidence (A2) study answering the question whether patients with acute musculoskeletal syndromes should be treated with paracetamol or NSAIDs.
Besides the question which drug is most effective in patients with acute musculoskeletal syndromes, even more important is the fact that the use of both drugs can have detrimental side effects.
Paracetamol is an analgesic and antipyretic, the exact mechanism of action is not known, but it should be used wisely, as it is one of the world's main causes of consecutive liver failure. Paracetamol is used frequently in home situations and is part of combination preparations without knowledge of many users.
NSAID's are drugs with analgesic and antipyretic effects and, in higher doses, they also have anti-inflammatory effects. They inhibit the enzyme cyclooxygenase (COX), which catalyzes the formation of prostaglandins and thromboxane. In the process of pain, prostaglandins cause local vasodilation and increased permeability of capillaries leading to edema. Other effects are increased sensitivity of local sensible nerves and stimulation of the temperature centre in the hypothalamus causing fever. The inflammatory

processes can cause damage in cartilage and bone tissue. As described in the "Farmacotherapeutisch Kompas", a publication of the CVZ (College voor Zorgverzekeringen), the indications for prescribing NSAID's are, among others, inflammatory-like and degenerative disorders as well as traumatic disorders as sprains and contusions. NSAIDs can have several potentially severe side effects, especially in older patients, such as GI bleeding, renal failure, bronchospasm and heart failure with additional medical costs. Annually, according to the HARM study in 21 Dutch hospitals, a considerable proportion of 5.6% of all unplanned admissions in Dutch hospitals is medication related. Internationally, these numbers are comparable. Half of these admissions are potentially preventable. The medications most often involved in these potentially preventable admissions are, besides anticoagulants, the NSAIDs. Reasons for hospitalization are mainly gastrointestinal tract problems (6.6% due to gastrointestinal bleeding) and cardiovascular problems. Of the potentially preventable admissions, 70% of the patients recovered completely, however 6.3% died and 9.3% experienced a disability after discharge and in 14% the outcome was uncertain at the time of discharge.
Besides the need for most effective treatment of pain after acute musculoskeletal syndromes, even more important is the safety profile of both medications mentioned. The hypothesis of our study is: paracetamol is as effective as an NSAID, but with a lower incidence of adverse events.
If the current study can point out that paracetamol is as effective as an NSAID in treating acute musculoskeletal injuries, this could be a very useful supplement to the guideline of the CBO and an evidence based way of decreasing additional costs of the use of NSAID's and their adverse events.

Study objective

The objective of the current study is to compare three different strategies of pain management in patients presenting to an emergency department and to a general practice with acute musculoskeletal syndromes (defined as musculoskeletal complaints after sustaining an injury with exclusion of a fracture). The strategies of pain management which will be compared are paracetamol, diclofenac and the combination of paracetamol and diclofenac.

Study design

It will be a double-blind, randomized controlled trial with a non-inferiority and superiority design.

Randomization
Blinded for the recruiter, the physicians and nurses and all other staff and personnel, as well as the patients themselves, patients are allocated to one of the three pharmacological treatments in a randomized fashion using a computerized randomization scheme. In order to ensure equal treatment allocation in the groups of subjects younger and subjects older then 60 years,

block-randomization is used. All patients are analyzed on an intention-to-treat basis.

Study medication
The moment of the first pain score and subsequent administration of the study drugs is marked as T0. All study drugs will be administed orally. All tablets will have a uniform appearance, prepared in advance by the pharmacy. Distribution and control of the study medication at the emergency department as well at Gezondheidscentrum Gein is the responsibility of the pharmacy of the AMC, experienced with studies involving medication. The patients will receive two tablets X and one tablet Y. Tablet X will contain paracetamol 500 mg or paracetamol-like placebo. Tablet Y will contain diclofenac 50 mg or diclofenac-like placebo. Because the packages containing the study drugs are prefabricated, possible combinations that the patients can receive will be:
1. paracetamol 1000 mg + diclofenac-like placebo.
2. paracetamol 1000 mg + diclofenac 50 mg.
3. paracetamol-like placebo + diclofenac 50 mg.

By producing the packages in advance in the pharmacy, the combination of paracetamol-like placebo and diclofenac-like placebo is ruled out, as it is deemed unethically to withhold patients pain medication in painful injuries. Besides these drugs, all patients will receive a Proton Pump Inhibitor (PPI); Omeprazol 20mg orally, this will not be blinded.
The CBO guideline "Use of NSAIDs and prevention of peptic injury" advises prescribing PPIs in all patients older then 70 years; a past history of peptic ulcer or untreated H. pylori infection. The guideline also states that a PPI should be administered when prescribing NSAIDs in patients 60-70 years old; use of anticoagulants; severe rheumatoid arthritis; heart failure or diabetes; use of corticosteroids or Selective Serotonine Re-Uptake Inhibitors (SSRIs). As we aim to treat all patients the same, we choose to administer the PPI to all study subjects. The alternative would be to exclude all patients with higher risk of NSAID-related GI-events, however, as we are highly interested in the group of elderly patients in a subgroup analysis, this is not feasible.
On discharge, patients will receive a package of study drugs. This package will contain the same combination of (blinded) study medication as they got in the emergency department or in the general practice, but it will be according to a schedule during three consecutive days. They will take two capsules X four times a day and capsule Y three times a day. Possible combinations will be:
1. 4x Paracetamol 1000 mg + 3x Diclofenac-like placebo
2. 4x Paracetamol 1000 mg + 3x Diclofenac 50 mg
3. 4x Paracetamol-like placebo + 3x Diclofenac 50 mg
This means all patients will take home a package of 22 capsules X and 8 capsules Y, which they will be advised to use during three days. Besides this, the patient will use a PPI (Omeprazol 20mg once daily) during these three days.

Data collection
Besides all baseline characteristics and occurrence of adverse events, the

primary outcome, pain, will be measured using the Numeric Rating Scale (NRS) on a standardized form by the treating physician, the research or treating nurse or a research associate, who are all trained in and educated about the study. Pain will be measured at time of inclusion and at fixed times (30, 60 and 90 minutes after study drug administration). Pain scores will be measured in rest and with active or passive movement of the extremity involved. When pain relief is insufficient and the patient / treating physician would like to give additional pain medication, this is documented. The choice of the additional pain medication is on the discretion of the treating physician (for example Tramadol or Morfine orally; or Fentanyl or Morfine IV in the emergency department). When deemed necessary by the treating physician, the randomization code can be revealed and the study drugs unblinded. As the alternative pain medication is frequently used in daily practice, the latter is not expected to occur.
At the same fixed intervals as the pain scores, the patients will be asked for potential adverse events. After recording the final set of pain scores and questions regarding potential adverse events the patients are discharged home, as soon as regular care is also finished. Patient satisfaction about pain relief will be documented using a 5-point Likert scale.
All patients will also receive a pain diary. This is a booklet in which the patients can record their own pain scores using the NRS and potential adverse events they experience while using the study drugs. All will be on standardized forms. Patients are instructed on how to use the diary and how to record the pain scores and potential adverse events. They will also receive information regarding contacting an independent physician with questions about the study or termination of participation. They will receive instructions on what to do when adverse events will happen or when pain management is insufficient. After 1-3 days after discharge the patients will be contacted by a research nurse or research associate (who are also blinded to the study medication) to evaluate all recorded data and the diary is obtained by the nurse or associate. After 5-8 days a house visit is planned, or a telephone call is made to evaluate the clinical course. After one month, the research assistant will have contact with the patients for the last time to fill in the EQ5D questionnaire. After this contact, the study ends for the patient. In the economic evaluation, factors that are analyzed are medication costs, need for additional pain medication, occurrence of adverse events and incidence of hospitalization due to medication related adverse events.

Intervention

The three possible interventions patients can be allocated for are (as described above under the section 'Study design');
1. Paracetamol 1000mg + Diclofenac-like placebo
2. Paracetamol-like placebo + Diclofenac 50mg
3. Paracetamol 1000mg + Diclofenac 50mg
All study drugs are blinded for the patient, the treating physician and all other research or clinical staff. Besides this study medication, all patients

will receive Omeprazol 20mg (not blinded). All study drugs will be administered orally.

After discharge from the Emergency Department or the General Practice, patients will take the same combination of (blinded) study medication as they already received, according to a schedule during three consecutive days. The three different schedules will be:
1. Paracetamol 1000 mg four times daily + Diclofenac-like placebo three times daily
2. Paracetamol-like placebo four times daily + Diclofenac 50 mg three times daily
3. Paracetamol 1000 mg four times daily + Diclofenac 50 mg three times daily
All study drugs are blinded, except for the Omeprazol 20 mg, which all patients take once daily during the three days they take the study medication.

Study burden and risks

All patients who participate risk the occurrence of known side effects of the drugs allocated for, as described in the Investigator*s Brochure text. This risk is the same as in daily practice and probably even smaller, as all individuals will receive proton pump inhibitors to protect patients from gastric damage from the NSAID*s.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- adult patients aged * 18 years
- non-penetrating limb injury, meaning a painful, acute strain, sprain or contusion of an extremity
- trauma occurred within 48 hours before presentation

Exclusion criteria

- previous treatment with analgesia for the same injury
- self inflicted injury (*auto-mutilation*)
- presence of wound, joint dislocation, fracture or more then one injury
- daily use of paracetamol and/or NSAID*s and/or other analgesia within two weeks before presentation
- patients with chronic pain
- previous adverse reaction or known allergy to paracetamol, NSAID*s or omeprazol
- pregnancy
- previous gastro-intestinal hemorrhage or perforation after NSAID use
- active or recurrent peptic ulceration or peptic bleeding (2 or more evident episodes)
- previous exacerbation of asthma after use of NSAID*s or acetylsalicylic acid
- severe cardiac failure
- liver cirrhosis
- severe renal insufficiency (eGFR<30mL/min)
- bone marrow depression or blood dyscrasia (active or in past medical history)
- combined use of angiotensin converting enzyme inhibitors (or angiotensin receptor blockers) AND diuretics
- physical, visual or cognitive impairment or non-Dutch language speaking (unable to use NRS, pain diary or EQ5D questionnaire)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-07-2013
Enrollment:	547
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Diclofenac
Generic name:	Diclofenac
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Omeprazol
Generic name:	Omeprazol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paracetamol
Generic name:	Paracetamol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28823
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2013-000381-11-NL
CCMO	NL42823.018.13
OMON	NL-OMON28823