The effects of propranolol on fear of tooth removal: A randomized, placebo-controlled, double-blind, parallel design trial

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The aim of this study is to determine the effects of propranolol on patients* crucial fear-related memories and dental trait anxiety in those undergoing surgical removal of one of their teeth or molars. The hypotheses that are tested are that...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Anxiety disorders and symptoms
Study type	Interventional

Summary

ID

NL-OMON45112

Source
ToetsingOnline

Brief title
Is propranolol effective against dental fear ?

Condition

- Anxiety disorders and symptoms
- Head and neck therapeutic procedures

Synonym
(Dental) anxiety; (Dental) phobia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: dental anxiety, memory, phobia, propranolol

Outcome measures

Primary outcome

- S-DAI score (short version of the Dental Anxiety Inventory)

- emotional intensity and vividness of the traumatic memory that is presumed to

have caused the anxiety for tooth extraction

Secondary outcome

- trauma-related (PTSD) symptom severity on a continuous scale the Dutch

version of the Impact of Event Scale (IES; Weiss & Marmar, 1997) will be used.

- the number of participants that meets the criteria for a specific phobia for

dental treatment (as confirmed by the M.I.N.I. plus questionnaire)

- degree of state anxiety

- degree of trait anxiety

- Physiological parameters; heart frequency and blood pressure

Study description

Background summary

Tooth or moval removal is considered to be the most common distressing surgical procedure practiced in oral and maxillofacial surgery (Earl, 1994; Oosterink, de Jongh, Aartman, 2008; Yusa et al., 2004). In a recent study in which patients were prospectively monitored until 4 weeks after their third molar removal, postoperative levels of dental anxiety were found to be significantly

associated with the level of emotional distress (i.e., pain, anxiety, or emotional disturbance) experienced during treatment (De Jongh et al., 2008). The results further suggest that whether a third molar removal results in a long-lasting heightened level of anxiety largely depends on the magnitude of past exposure to aversive dental situations. The combination of frequency of previous exposure to distressing dental events and preoperative anxiety level appeared to significantly predict the level of anxiety 4 weeks after treatment, accounting for 71% of the variance. In 8% of the patients symptoms indicative of posttraumatic stress disorder (PTSD) developed, which are generally observed in response to typical life-threatening events, such as witnessing or being the victim of rape or assault or being exposed to a disaster (American Psychiatric Association, 2000). PTSD symptom severity assessed 4 weeks after third molar removal was significantly associated with pain scores during treatment, which suggests that the experience of pain has the potential to increase such risk. Thus, distressing or traumatic experiences are likely to make patients vulnerable, thereby increasing the risk for long-standing dental anxiety and trauma-related symptoms developing in response to a distressing event. Evidence for the contention that exposure to distressing experiences increase the likelihood of developing dental anxiety comes from studies showing that a high percentage of anxious dental patients indicate having experienced one or more terrifying dental treatment events that could explain the onset of their dental fear or phobia (Locker, Liddell, Dempster, & Shapiro, 1999; De Jongh, Fransen, Oosterink-Wubbe & Aartman, 2006). To this end, the experience of helplessness appears to have the greatest potential risk of precipitating pathological forms of dental anxiety (Oosterink, De Jongh & Aartman, 2009). As individuals tend to construct highly negative images and dysfunctional cognitions of such events (De Jongh & Ter Horst, 1993; De Jongh et al., 1994), phobic individuals, like those suffering from posttraumatic stress disorder (PTSD), are likely to experience excessive retrieval of fearful memories of past horrific events (De Jongh, Aartman & Brand, 2003). Research indicates that such memories are difficult to suppress (De Jongh et al., 1996; Muris et al., 1998), and as phobias are characterized by fear networks of high associative strength, confrontation with a phobic stimulus may provoke retrieval of stimulus-associated fear memories with a strong physiological response (Cuthbert et al., 2003; Foa & Kozak, 1986; Lang, 1985). Research supports this notion showing that images of previous distressing events, and associated negative beliefs, are not only triggered by a direct confrontation with a phobic object or situation, but also in anticipation of such an event, and can even occur spontaneously (De Jongh, Fransen, Oosterink-Wubbe & Aartman, 2006). There are indications that every reactivation of such aversive experiences further strengthens the aversive memory trace (De Quervain & Margraf, 2008). This means that activation of aversive memories not only plays an important role in the symptomatology of fears and phobias, but also in the process contributing to the maintenance, and aggravation of these symptoms.
Last century much progress has been made in understanding the process of consolidation and re-consolidation of memories (Cahill & McGaugh, 1998; Lechner et al., 1999). In this process a brain structure termed the amygdala is

crucial since it is involved with the formation of enhanced declarative memory for emotionally arousing events (Cahill & McGaugh, 1998; McGaugh, 2000; Phelps, 2004). In a threatening situation adrenaline and noradrenaline (or epinephrine and norepinephrine) are released by the adrenal medulla, which mediates the body's short term stress response, leading to orthosympathetic activity such as vasoconstriction, increased heart rate, a higher blood pressure and sweat production. Adrenaline is also released as a neurotransmitter in the brain.
This stress hormone leads to a state of alertness and has been found to modulate the processing of emotional information via the amygdala (van Stegeren, 2008). What is less known is that the endogenous stress hormones feed back directly to the amygdala to strengthen the long term memory of the same events that initially induced their release (Cahill, 2003). As adrenaline seems to enhance memory in a dose-dependent way, the subsequent release of glucocorticoids (the *second wave* of the adrenocortical response) dose-dependently strengthens the memory enhancing effects of adrenaline, having an important adaptive function in response to stressful experiences(Tronson, & Taylor, 2007). That is, in addition to give rise to an immediate response to an emotional event, these hormones aid future responses by enhancing declarative memory of this event.
A large proportion of people suffer from conditions that result from trauma and the disturbing effects of how it is remembered. Both PTSD and dental phobia are excellent examples of such conditions. In order to effectively treat these disabling conditions it would be necessary to be able to transform the way this experience has initially been encoded. This would require some type of intervention that blocks or diminishes the human stress response as this would help reconsolidating the memory of an emotionally powerful experience into a less emotionally charged form, resulting in less re-experiencing and thus in a reduced fear response. There is evidence to suggest that the ß-adrenergic blocker propranolol is physiologically capable of doing this.

Study objective

The aim of this study is to determine the effects of propranolol on patients* crucial fear-related memories and dental trait anxiety in those undergoing surgical removal of one of their teeth or molars. The hypotheses that are tested are that individuals who received 80 mg propranolol one hour rpior to the removal of their teeth, and 40 mg propranolol immediately after removal, compared to individuals in the placebo-control condition, would report:
1. a significantly lower level of state anxiety during treatment.
2. a significantly lower level of state anxiety in anticipation on a next appointment.
3. a significantly lower level of dental trait anxiety at four weeks follow up.
4. significantly less brightness, emotional intensity, aversiveness and intrusiveness of the memory of which patients indicated to be significantly associated with their fear of dental or oral surgical procedures, both immediately after the treatment than at four weeks follow-up.
5. significantly less brightness, emotional intensity, aversiveness and

intrusiveness of the memory of their (first) tooth removal, both immediately after the treatment than at four weeks follow-up.
6. significantly less physiological arousal (i.e. heart rate, blood pressure and skin conductance) four weeks after the procedure.

In addition, it is hypothesized that the reductions related to these variables (difference between scores before and at four weeks follow-up) of patients of the propranolol condition would be significantly greater than those of the placebo control condition.

Study design

Seventy patients with excessive fear for tooth removal will be randomly allocated to two groups. Both groups of participants will undergo (regular) tooth or molar removal. One group of receives propranolol pills before and after treatment, whereas patients in the other group will receive exactly similar looking placebo pills. An independent researcher who is blind to group allocation will assess all participants' scores on standardized outcome measures; before and after completion of the tooth or molar removal, and finally after completion of treatment (at the second tooth or moral removal: a follow-up appointment without research intervention).

Intervention

One hour prior to their treatment during which a tooth will be removed, patients receive 80 milligrams of propranolol. Propranolol is a beta blocker which previously has been shown to be effective in terms of reducing state anxiety in people who were given a dental anesthetic injection. After the removal of their teeth patients receive a second dose of 40 milligrams with the intention to reconsolidate the effect of propranolol on the of the wisdom teeth removal memory.

Study burden and risks

Propranolol is a relatively safe drug that is commonly prescribed. The main side-effects include gastroinestinal symptoms (nausea, diarrhea), fatigue, impotence, decreased concentration, reduced responsiveness and headache; in addition, there may be pharmacological effects inherent to *-blockers (bronchospasm, bradycardia, heart block, hypotension and dizziness, heart failure and cold, cyanotic extremities).

Propranolol should not be used in patients with bronchial asthma, other obstructive pulmonary disease or a history of bronchospasm. Other contraindications include hypersensitivity to propranolol, bradycardia, cardiogenic shock, hypotension, metabolic acidosis, second and third degree AV block, sick sinus syndrome, untreated phaeochromocytoma, prolonged fasting and

heart failure. Pregnant and lactating women are excluded from this study. This applies to the entire study.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Excessive anxiety for necessary tooth and/or molar extraction
2. Age above 18 years.

Exclusion criteria

1. Systolic blood pressure < 100mmHg;

2. Allergic asthma, Decompensatio cordis, Cardiac arrythmia or Insulin-dependent diabetes;
3. Previous adverse reaction to a beta-blocking agent;
4. Use of another beta-blocking agent;
5. Pregnant or breast feeding;
6. Being in psychotherapy elsewhere;
7. Renal failure.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-11-2014
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.a.
Generic name:	Propranolol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	05-03-2014

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2018
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: 28388
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2013-004798-29-NL
Other	Nederlands Trialregister (TC = 2398)
CCMO	NL42210.018.13
OMON	NL-OMON28388