A randomized, controlled, equivalence study of authorized versus non-authorized deception in a model of pain following third molar extraction

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Abstract

Background and rationale: When deception is used, a conflict ensues between the need to use it to answer a research question scientifically whilst protecting the participants' autonomy simultaneously. Authorized deception (where participants are told they will be deceived) is a method that has been proposed to address the traditional "non-authorized" deception. Our study evaluated authorized versus non-authorized deception in a pain model of third molar extraction.

Methods: Adult patients requiring surgery for third molar extraction were enrolled after consent and randomized to either the authorized or "non-authorized" deception group. Within each group, they were further randomized to receiving either an "expensive" or an "inexpensive" painkiller. All participants actually received the same painkiller. The primary outcome measure was pain, while the proportion of patients taking rescue medication was the secondary outcome measure. All patients were debriefed at study completion.

Results: The median peak pain score was not significantly different between the groups. A little over 21% patients in the authorized deception group relative to 32.4% patients in the non-authorized group took rescue medication (p = 0.09). In the non-authorized deception group, 30% patients in the "inexpensive" group relative to 34.5% patients in the "expensive" group took rescue medication (p > 0.05). In the authorized deception group, 12.5% patients who received "expensive" relative to 30.4% who received the "inexpensive" painkiller took rescue medication (p = 0.04).

Conclusions: While our study showed equivalence of the two deception modalities, authorized deception may not be truly sterile.

Keywords

Authorized deception, unauthorized deception, patient safety, ethics, third molar extraction

Introduction

Deception, also called as "misleading falsehood," has a long history of use in clinical research. The Tuskegee syphilis study[1] and the Milgram obedience to authority experiments[2] are among the earliest examples and both attracted worldwide criticism and condemnation. The Tearoom Trade Study where a researcher provided false information about his identity in order to covertly understand men's sexual behaviors in public restrooms generated both methodological and ethical debates.[3]

Deception in clinical research is, however, a successful tool too and stems from the fact that response to any intervention has two components: (a) the effect of the intervention per se and (b) the effect of the *expectation* that the intervention will work (or otherwise).[4] A study by Espay *et al.* is an example of this. Patients with Parkinson disease were told they would receive either a "cheap" or an "expensive" "novel" dopamine agonist and it was seen that both infusions improved

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motor function with the response being greater with the "expensive" medication.[5] In reality, all patients received normal saline.

Wendler and Miller have defined deception as occurring when investigators communicate with research participants in a manner that produces false beliefs. This can be done in one of two ways – (a) giving false information or (b) withholding information.[6] With the use of deception, a conflict ensues between the need to use it to answer a research question scientifically whilst protecting the participants' autonomy at the same time. Its use precludes the participant having full knowledge about the exact nature of the research proposal and undermines the informed consent process.

The method currently in use to mitigate the moral harm of deception in studies is to debrief participants at the end of the study and tell them that they were deceived. This unfortunately becomes post facto. One way to actually protect participants' autonomy is to use the process of *authorized deception* whereby participants are told that they would be deceived in some way, but the exact nature of the deception is not actually revealed to them, thus maintaining scientific validity and yet protecting autonomy.[4] The informed consent forms used in authorized deception also indicate this and include a statement that the participants would be debriefed at the end of the study about the exact nature of the deception. A review of deception literature in PubMed revealed only one randomized, controlled study that used authorized deception,[7] which showed the equivalence of authorized deception with the more traditional "non-authorized" deception in an experimentally induced pain model.

Against this backdrop, we carried out the present study with the primary objective of evaluating authorized versus non-authorized deception in a pain model of third molar extraction. A secondary objective was to assess if the perception of the cost of the painkiller impacted response to it.

Methods

Ethics, trial registration, choice of pain model and study period

The study protocol was approved by the Institutional Ethics Committee of the Seth GS Medical and King Edward Memorial Hospital, Mumbai, and the study was prospectively registered with a Clinical Trials Registry. The pain model chosen was that of pain following extraction of the third molar and is a model used by the pharmaceutical industry for submission of studies that evaluate novel analgesics for regulatory approval to the US FDA.[8] The study was conducted from April 2017 to April 2018 at a tertiary referral center. The senior authors conceived the study, wrote the protocol, defended it with the institutional ethics committee (IEC) including a formal presentation and defense in the IEC meeting and had complete oversight of the study.

Study design, inclusions and exclusions

The study was designed as a randomized, controlled, equivalence design study with the null hypothesis being that authorized deception is not equivalent to non-authorized deception, and the alternate hypothesis being that the two are equal. Adult patients over the age of 18 years, who required surgery for an impacted third molar (as per Winter's classification)[9] and consented were included. Patients with a history of allergy to non-steroidal anti-inflammatory drugs, those with a history of coagulation or platelet disorders and chronic smokers were excluded.

Randomization, allocation concealment and the informed consent process

Participants were first randomized to either the authorized or the non-authorized deception group in a 1:1 ratio. This randomization was known only to the physician who saw the patient. Subsequently, within each group, there was a next level of randomization to receive either an "inexpensive" or an "expensive" painkiller following the surgery. This second randomization was kept in a sealed envelope and opened by the treating physician in front of the patient. What was inside the envelope was not known either to the physician or the patient until such time that the envelope was actually opened (see later for more details).

Both sets of randomization sequences were simple randomization and generated using the website www.randomization.com. Allocation was concealed for the second level of randomization using sequentially numbered opaque sealed envelopes.

The senior authors prepared both the randomization lists, and the first randomization list was visible only to them. They shared the second randomization list with all the authors so that it would help them allocate patients into either the authorized or non-authorized deception groups in the dental outpatient clinic. There was no allocation concealment for this list.

There were two different participant information sheets and informed consent forms according to whether the patient got allocated to the authorized or non-authorized deception groups. Once a patient was found eligible, authors at the dental clinic viewed the list made by the senior authors to see which group that patient

went into. If it was the authorized deception group, the patient was given the consent form that was specific for that group. This consent form stated the following

> This is a research study that is evaluating the efficacy of two pain killers – one that is expensive and the other inexpensive. In this study, you will be deceived in some way. We are at this point, however, unable to reveal the exact nature of the deception to you but please note that this is needed for the study. We will reveal the exact nature of the deception at the end of the study and debrief you. Please note that the you will be receiving standard of care for your treatment and are free to opt out of the study without affecting your management now or in the future at this institute. Do also note that that Institutional Ethics Committee that is an independent body and that safeguards the rights, safety and wellbeing of research participants has approved this study.

This was followed by the other regular elements of the consent form.

If an eligible patient went into the non-authorized group, he/she was given a regular consent form which did not address deception in anyway and merely stated that "*This is a research study that is evaluating the efficacy of two pain killers – one that is expensive and the other inexpensive*" followed by other regular elements of the consent form.

The consent forms were in the language the patient best understood. After the participant accorded consent (either authorized or non-authorized deception – that is knowing they would be deceived or not but neither knowing what the deception was about), and the investigators determined by opening the sealed envelope that contained the allocation code for that patient, the patient was "allocated" to either the inexpensive or expensive groups. Participants in both groups merely saw a slip of paper that said "inexpensive," or "expensive." If the former, the patient was given medications labelled "inexpensive." If the latter, the patient was given medications labelled "expensive." The study procedure is depicted schematically in Figure 1.

The nature of deception

Both sets of painkillers, regardless of their labelling as "inexpensive" or "expensive" came from the same batch, had the same manufacturer, had the same expiry *and were standard of care at the institute and merely labelled as "inexpensive" or "expensive."* This was the deception and was restricted to the painkiller used and not the other medications – antibiotic and anti-acid medications.

Study medications

The standard of care followed at our institute is to use a combination of antimicrobials, analgesics and anti-acid medications following third molar extraction. All patients were started on a combination of Tab amoxycillin + clavulinic acid (500 mg orally every 12 h) a day prior to surgery and asked to continue this for a total of five days. A fixed dose combination of diclofenac (50 mg) + paracetamol (325 mg) + serratiopeptidase (10 mg) twice a day was given as the analgesic medication. Tramadol (50 mg) single dose formed the rescue medication, and patients were asked not to exceed 200 mg of tramadol per day.

Outcome measures and end of the study

The primary outcome measure was the pain recorded on a visual analogue scale (VAS) with 0 depicting no pain and 10 depicting extreme pain. Patients were asked to record pain every 6 h on a diary card. The proportion of patients who took rescue medication, duration of surgery, mouth opening post-surgery (measured in mm using a motion scale that could be inserted into the mouth and recorded 2 h following surgery and 6 h later) were the secondary outcome measures. The study ended 24 h post-surgery when the participants reported to the dental clinic for a follow-up. The diary cards were collected from them at this point and debriefing was done.

The process of debriefing and the exit feedback

When the participant came back to the dental outpatient clinic for his follow-up 24 h post-surgery, patients in the authorized deception group were told about the exact nature of the deception. In the non-authorized group, the patients were told that they were deceived by giving false information, as the idea was to see if the cost of medication impacted their pain perception. They were then asked their views about the study – did they feel hurt, cheated or taken for granted? What was their impression of the study itself and the investigator? Would they consider participating in similar studies in the future?

Sample size calculation

This was based on the VAS score, the primary endpoint. Assuming an equivalence margin of 1, a standard deviation of 2, at 80% power and 5% significance, a total of 90 patients per group (authorized versus non-authorized groups) were needed to prove equivalence.
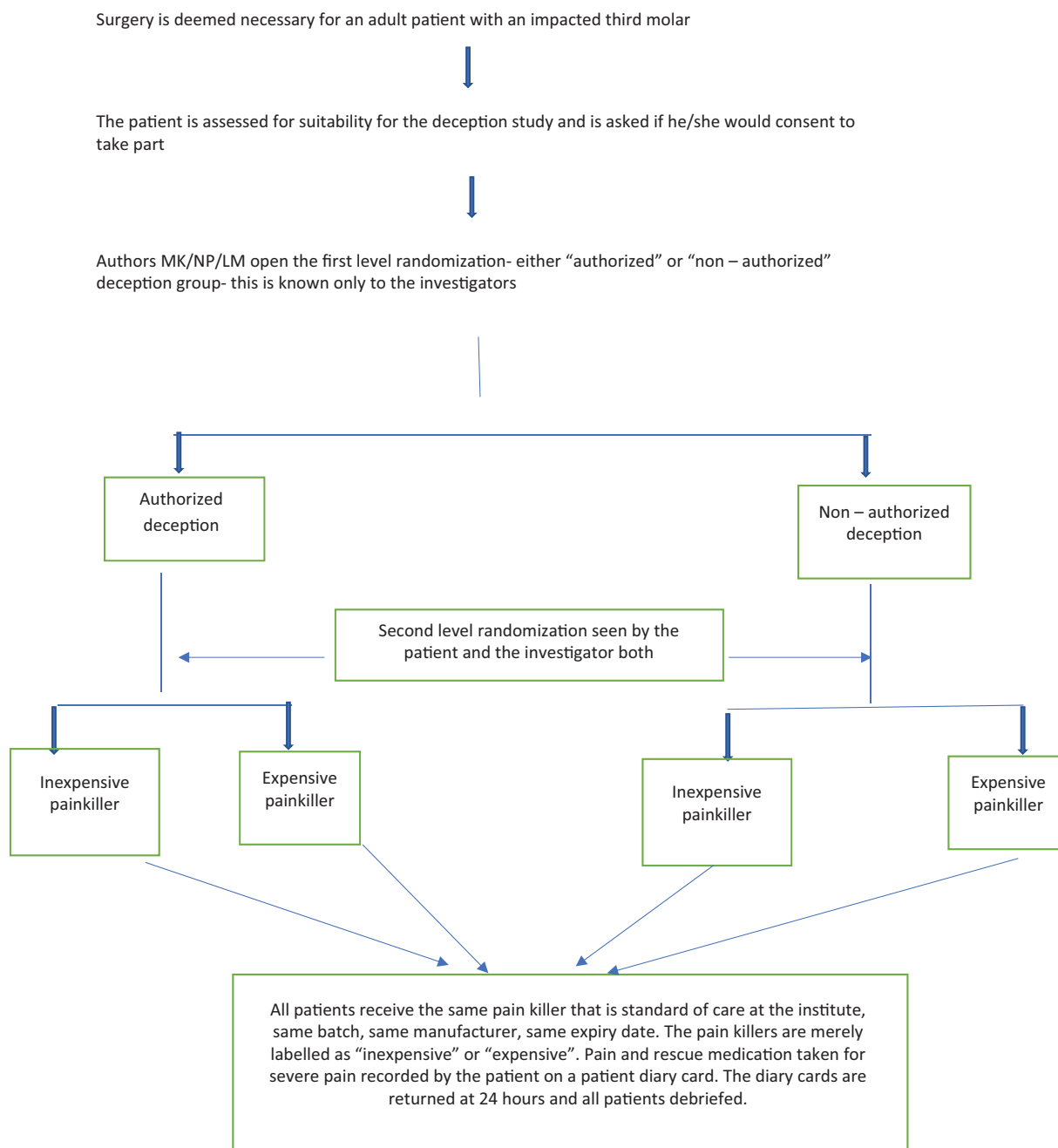
Surgery is deemed necessary for an adult patient with an impacted third molar

The patient is assessed for suitability for the deception study and is asked if he/she would consent to take part

Authors MK/NP/LM open the first level randomization- either "authorized" or "non – authorized" deception group- this is known only to the investigators

Authorized deception

Non – authorized deception

Second level randomization seen by the patient and the investigator both

Inexpensive painkiller

Expensive painkiller

Inexpensive painkiller

Expensive painkiller

All patients receive the same pain killer that is standard of care at the institute, same batch, same manufacturer, same expiry date. The pain killers are merely labelled as "inexpensive" or "expensive". Pain and rescue medication taken for severe pain recorded by the patient on a patient diary card. The diary cards are returned at 24 hours and all patients debriefed.

Figure 1. Schematic representation of the study procedure per CONSORT flowchart.

The free online calculator https://www.sealedenvelope.com/power/continuous-equivalence/ was used for this purpose. In addition, we added 15% for drop-outs, giving us a total sample size of 212 participants or 106 participants per group.

Statistical analysis plan

Quantitative data such as age are expressed as median (range) and qualitative data such as number of participants who took rescue medication as proportions. Both within- and between-group comparisons were made for the VAS score, peak pain score and the proportion of patients who took rescue medications. The VAS and peak pain score were analyzed using ANOVA, while rescue medication was analyzed using the Fisher's exact test. A descriptive synthesis of the responses to debriefing was done. All analyses were done at 5% using Graphpad Instat 3.06. Only those patients who completed their 24-h follow-up and submitted their diary cards were analyzed (per-protocol analysis).

Results

Demographics

A total of 222 consecutive patients were enrolled in the study, of which 97 were males and 125 were females. The median (range) age was 38 years (21–60). The median (range) duration of surgery was 25 min (15–45). There was one consent refusal only, and the patient was in the non-authorized deception group. Three patients were lost to follow-up and finally 112 in the authorized deception and 105 in the non-authorized group were available for the per-protocol analysis.

Between-group analysis

The median (range) pain score in the two groups was similar (2 (0–10) in the authorized deception group versus 3 (0–10) in the non-authorized deception group), and the between-group difference was not statistically significant (p > 0.05). Similarly, the peak pain score between the groups was also not significantly different (p = 0.19).

A total of 24/112 (21.4%) patients in the authorized deception group relative to 34/105 (32.4%) patients in the non-authorized group took rescue medication, and this difference was also not significantly different (p = 0.09).

Within-group analysis

The median peak pain score between the "inexpensive" versus the "expensive" arms of the both deception groups was also not significantly different. With regard to rescue medication, in the non-authorized deception group, 15/50 (30%) patients in the "inexpensive" group relative to 19/55 (34.5%) patients in the "expensive" group took rescue medication (p > 0.05). However, in the authorized deception group, 7/56 (12.5%) patients who received the "expensive" relative to 17/56 (30.4%) who took the

"inexpensive" painkiller took rescue medication, and this difference was statistically significant (p = 0.04).

Details of the pain score and rescue medication in the two main groups and subgroups are depicted in Table 1.

Responses to debriefing

Mixed responses to debriefing were obtained. A total of 87/112 (78%) in the authorized and 85/105 (81%) in the non-authorized group said that they "didn't feel hurt or cheated or taken for granted" in anyway. One patient in the authorized deception group and five in the non-authorized deception group wondered why deception was at all needed in clinical research. A total of 66/105 (63%) patients in the non-authorized deception group felt that they could have been told that they were being deceived in some way, i.e. indicating a preference for authorized deception. The remainder 37% felt that non-authorized deception was a useful research tool. In the authorized deception group, 94/112 (83.9%) said that it was good that they knew at least in part that they were being deceived, while the remainder felt that they would not have minded being in the non-authorized deception group. The majority of patients in both groups (97/105; 92.4%; non-authorized) and 102/112 (91.1%, authorized) said that they would not mind participating in similar studies in future and said that they did not harbor any ill will against the investigators.

Discussion

The present study evaluated authorized versus non-authorized deception in a randomized, controlled, equivalence design in a pain model of third molar extraction and found that with regard to the primary objective of pain, there was no difference seen between the two groups. In the non-authorized deception group, neither the pain score nor the uptake of rescue medication differed between the groups given

Table 1. Details of pain scores and rescue medication used in the groups.

	Authorized deception			Non-authorized deception		
	Inexpensive painkiller n = 56	Expensive painkiller n = 56	p	Inexpensive painkiller n = 50	Expensive painkiller n = 55	p
Median (range) pain score	2 (0–10)	2 (0–10)	0.31	3 (0–10)	3 (0–10)	0.36
Proportion of patients (%) of the total who took rescue medication	17/56 (30.4%)	7/56 (12.5%)	0.04	15/50 (30%)	19/55 (34.5%)	0.68

Note: p values for both median pain scores and rescue medication for the between-group analysis were not statistically significant, p > 0.05.

"expensive" versus "non-expensive" painkillers. The authorized deception group, however, had a significantly lower proportion of patients (p = 0.04) who took rescue medication (the secondary objective) in the "expensive" painkiller group relative to the "inexpensive" group.

Patients' expectations for improvement, also referred to as "response expectancies," are thought to be one of the central mechanisms responsible for placebo effects[10–12] and are what are classically addressed in studies that use deception to answer a research question. Miller *et al.*[4] were the first to attempt to make deception compatible with informed consent by proposing the concept of authorized deception. The problem with deception lies in the fact that informing the patients about deception will not permit the study to be conducted and will affect its scientific rigor, while deceiving the participants would make a fully informed consent impossible to achieve. Authorized deception, they argued, would bridge this gap to an extent. In this process, participants would be told *a priori* that the experimental procedures would not be described to them entirely or accurately and that some features of the procedures will be misleading or deceptive. Martin and Katz[7] evaluated the use of authorized versus non-authorized deception in a model of experimentally induced placebo analgesia. The use of the former was shown not to impact the magnitude of the placebo effect, recruitment and retention of participants and did not lead to any significant psychological harm. A majority of the participants studied also preferred this modality of deception to the classical non-authorized deception. While our study is similar in terms of no difference with regard to pain perception between the two modalities of deception, it is different in terms of responses to debriefing which were mixed. Some preferred it, while others stated that deception was quite alright, as the treating physician would not let any harm come to them. This difference seen in debriefing may be explained by the fact that the nature of the doctor–patient relationship in India is still largely paternalistic with the dominant force in the relationship being the physician, and the patient deriving considerable comfort by leaving the burden of worry and decision making to the physician and trusting him implicitly.[13]

A comparison of our study with that of Espay *et al.*[5] showed striking differences. The Espay study used non-authorized deception only and evaluated the impact of the cost on symptomatic improvement in patients with Parkinson disease. Normal saline was given to 12 patients and labelled as being either an "expensive" novel dopamine agonist or a "cheap" dopamine agonist, with the former eliciting a much better symptom improvement. This can be compared with our non-authorized deception arm where we did not see any difference either in the pain scores or in the proportion of patients using rescue medication in the "expensive" versus the "inexpensive" painkiller group (we did not, however, use the term "cheap" painkiller in our study). Given that there were no patent laws up to January 2005 in the country, the generic drug industry flourished and each generic in the country today is marketed under a particular brand name leading to a wide range of *branded generics*. The lack of difference may be attributed to a long-standing generic drug industry that manufactures quality products at considerably lower costs,[14] and thus no difference was seen in the patients' perception of cost as a factor in the response to the painkiller. Our study, however, was not powered to assess a perception difference between innovator drugs and branded generics, and this finding would need to be confirmed in another study.

Our study threw up an unexpected finding within the authorized deception group. Significantly, (p = 0.04) more patients on the "inexpensive" painkiller (30.4%) needed rescue medication relative to much fewer patients on the "expensive" painkiller (12.5%). The former is in line with rescue medication intake in both arms of the non-authorized deception group. One possible explanation is that since they were told that they would be deceived, they did not expect the "inexpensive" painkiller to work and hence showed a greater intake of the rescue medication. Blease[15] argues that the use of authorized deception, however well meaning, may in fact incite a nocebo response, i.e. ignite the very problem we were hoping to extinguish. This is perhaps what happened in our study in the "inexpensive" arm of the authorized deception group and indicates that authorized deception may not be truly sterile and it may in fact impact the very core of deception, i.e. expectancy manipulation. The low use of rescue medication in the "expensive" arm of the authorized deception group is harder to explain and we are uncertain as to what could have happened. Although the difference was not statistically significant (p = 0.09), fewer patients overall in the authorized deception group (21.4%) took rescue medication relative to the non-authorized deception group (32.4%).

Is there a workaround to using deception in studies – either non-authorized or authorized? Balanced placebo designs and balanced cross-over designs have been evaluated as among the more effective ways to address the placebo effect that stems from response expectancy.[16] Another way is the more recent (albeit few) studies using "open label placebos."[17,18] The consent forms in these studies explicitly inform patients that they are receiving a placebo contrary to the traditional randomized controlled trial (RCT) where they are told that they may receive a placebo or may receive standard

of care. The study by Kelley *et al.*[17] in patients with a diagnosis of non-psychotic major depressive disorder randomized patients to either the open label placebo arm (using specially designed consent forms) or waitlist control and showed a difference of 0.54 units between the two groups at the end of two weeks on the 17-item Hamilton Scale for Depression which is larger than the effect size seen in classical drug – placebo RCTs. This model is, however, not feasible for pain studies, as using a placebo in pain studies would be unethical, and these studies would still need the traditional models of deception.

Our study is limited by the fact that we did not evaluate the mood of patients using standard questionnaires such as the Profile of Moods Questionnaire (POMS), as mood can impact short-term intervention effects.[19] We were also unable to interview our participants sometime after the study completion and debriefing. This would have helped particularly in the authorized deception group as to why so few opted to use rescue medication in the "expensive" arm and what they really thought of "expensive" versus "inexpensive." We could not do this, as the blinded results were analyzed only much later.

In summary, our study showed that with regard to the primary objective of pain scores, there was no difference between authorized and non-authorized deception in a pain model of third molar extraction. However, the secondary objective of rescue medication in the two groups which threw up contrasting results in the two groups needs exploration in other pain models. Also, the authorized deception group appears to be associated with a nocebo response and this would need be explored further to confirm that authorized deception truly does not impact patient expectancy.

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