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The effect of transmucosal 0.2mg/kg Midazolam premedication on dental anxiety, anaesthetic induction and psychological morbidity in children undergoing general anaesthesia for tooth extraction

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Short title: Midazolam 0.2mg/kg premedication

Summary

Background: The project aims were to evaluate the benefit of transmucosal Midazolam 0.2mg/kg pre-medication on anxiety, induction behaviour and psychological morbidity in children undergoing general anaesthesia (GA) extractions.

Method: 179 children aged 5-10 years (mean 6.53 years) participated in this randomised, double blind, placebo controlled trial. Ninety children had Midazolam placed in the buccal pouch. Dental anxiety was recorded pre operatively and 48 hours later using a child reported MCDAS-FIS scale. Behaviour at anaesthetic induction was recoreded and psychological morbidity was scored by the parent using the Rutter Scale pre-operatively and again one-week later. Subsequent dental attendance was recorded at one, three and six months after GA.

Results: Whislt levels of ental anxiety did not reduce overall, the most anxious patients demonstrated a reduction in anxiety after receiving midazolam premedicationmay (p=0.01). Neither induction behaviour nor psychological morbidity improved. Irrespective of group, parents reported less hyperactive (p= 0.002) and more prosocial behaviour (p=0.002) after the procedure:;, older children improved most (p=0.048), Post GA Dental attendance was poor and unrelated to after the procedure and unaffected by premedication..

Conclusion: 0.2mg/kg buccal Midazolam provided some evidence for reducing anxiety in the most dentally anxious patients. However, induction behaviour, psychological morbidity and subsequent dental attendance were not found to alter between the premedication groups.

Key words: general anaesthesia; dentistry; premedication; midazolam; anaesthetic induction; postoperative morbidity.

Introduction

The referral for dental general anaesthetic (DGA) is now deemed to be a treatment of 'last resort'[1] for children in advanced stages of dental disease who are too anxious, or too immature, to undergo dental treatment by other means [2]. The prospect of the DGA event has been found to provoke anxiety in 56-66% of children [3]. These children are more dentally anxious than their peers, and their anxiety is also associated with greater distress at anaesthetic induction and increased post-operative morbidity [4]. Psychological morbidity such as attention-seeking, tantrums, crying and nightmares is well recognised [5, 6] and is more likely in children who are younger, have pre-existing behavioural problems and pre-existing dental anxiety [3, 4]

Midazolam is a common premedicant at anaesthetic induction and is suggested thatto reduce post-anaesthesia behaviour disturbance. However, the evidence for efficacy varies between study populations and there is a balance between optimal therapeutic effect and delay of postoperative recovery [7, 8, 9].

The authors have already reported that the children in this trial experienced significant cognitive deficit due to midazolam premedication when compared with placebo [10]. This paper presents the data that evaluates the benefit of 0.2mg/kg Midazolam premedication on dental anxiety, anaesthetic induction distress, psychological morbidity and subsequent dental attendance.

Aims

To evaluate the benefit of Midazolam 0.2mg/kg deposited in the buccal pouch as a pre-medication upon child-reported dental anxiety, the observed behaviour of children at anaesthetic induction, post operative psychological morbidity and continued dental attendance.

Null Hypothesis (does the BDA require this?)

Pre-operative 0.2mg/kg midazolam will reduce neither anxiety, obstructive behaviour at the time of anaesthetic induction nor post operative psychological morbidity and will not facilitate subsequent dental attendance.

Method

A prospective, randomised placebo-controlled, double blind clinical trial (registration number ISRCTN: 12026431; CTA 8000/13014) was conducted. Ethical approval was granted by the Area Ethics Committee (LREC DENTAL23; R&D ref 03DN023).

Patients and recruitment

Children aged **5 to 10 years** attending Glasgow Dental Hospital and School (GDH&S) for extractions were invited to participate after the need for DGA had been determined at a previous assessment clinic. Following appropriate written consent, sampling was consecutive but limited by the capacity of the service and the availability of the research assistant (RA). Exclusion criteria included: patients who were not ASA I or II, those with learning disabilities, psychiatric disorder, non-fluency in English, or where the family had no telephone for follow-up.

Recruitment took place between October 2004 and January 2006, during which time 2495 children (aged 3-10 years) attended the service.

Randomisation and blinding

The randomisation occurred at the time of the DGA visit using an automated computerised system. The Research Nurse (RN) telephoned a dedicated line and obtained a treatment code for each subject. The general anaesthetic staff and the RA remained blind until the code was broken following the completion of data collection and input.

Premedication administration

The RN placed the medicine in the buccal sulcus using a needle-less syringe. The midazolam subjects each received 0.2mg/kg ('Epistat' preparation) whilst the placebo subjects received a similar volume prepared by the hospital pharmacy. The placebo pre-medication was designed to have a similar taste, texture and colour as the Epistat preparation. Children were encouraged to try not to swallow the medication but to allow mucosal absorption to occur. Approximately thirty minutes later, anaesthesia was induced by inhalation of sevoflurane, nitrous oxide and 40% oxygen and maintained with a similar mixture using a nasal mask or, occasionally though not routinely, a layryngeal mask. Whilst asleep, an intravenous cannula was inserted into the child's hand. The children were monitored using ECG and pulse oximeter. Before the extractions, lignocaine with adrenaline infiltrations were routinely injected into the buccal mucosa adjacent to the extraction site to reduce bleeding and to provide post-operative pain relief. The RN remained with the child throughout the procedure and until the child was fully recovered and assessed as fit to discharge.

Data Collection

All data werewere collected by the RA.

Demographic

Demographic information was collected from the parent at the time of recruitment. This included the level of social deprivation- 'DEPCAT' [11].

Dental Anxiety

Pre-operative: dental anxiety was assessed prior to the administration of the pre-medicament, using the Modified Child Dental Anxiety Scale (MCDAS) augmented by the Facial Image Scale (FIS). The MCDAS has eight dental anxiety items. The score in each question may vary from 1 (relaxed) to 5 (extremely worried), thus the total score may range from 5 to 40 and is well validated [12, 13]. In order to help the child confirm their response on the MCDAS, they were asked to indicate which facial expression on the FIS also corresponded to their answer (facial expressions on the FIS range from smiling/relaxed through neutral to worried/sad).

Due to the young age of the present participants, however, it was inevitable that many of the children lacked experience of some of the dental procedures referred to in the MCDAS. Items for which the child had no experience were therefore omitted completely. Then, in order to render the scores comparable across children who answered different numbers of items, the average score was calculated for each child (i.e. the sum of the scores for each of the individual answers, divided by the total number of answers). The resultant average scores (ranging from 0 – 5) were used to allow group comparisons.

It was also necessary to carry out a transformation of the MCDAS threshold scores for dental anxiety to equate them with the revised scoring procedure described above. were excluded if children failed to understand the question, or if they had not prior experience of the treatmenttoThe MCDAS norms classify scores of 8.8 as 'normal', scores of over 19 as 'anxious' and scores of over 31 as 'highly fearful' [12, 13, 15]. Transformation of these scores to a scale range of 0 to 5 results in In a score of 8.8 isbeing equal to 1.1, a score of 19 isbeing equal to 2.4, and a score of 31 isbeing equal to 3.9.

The MCDAS-FIS was repeated, using the same method outlined above, 48 hours later at a home visit.

Observed behaviour at anaesthetic induction

Observed behaviour at induction was recorded using the 'Houpt' scale [16, 17] as shown in Table 1. , and was augmented with further criteria relating directly to the anaesthetic induction such as mask acceptance.

Pre and postoperative emotional and behavioural assessment

The well validated and reliable Revised Rutter Scale for School-Age Children [18, 19, 20, 21] was completed by parents prior to premedication and at one week postoperatively by telephone. This scale describes parental ratings of their children's behavioural and emotional difficulties and provides both a Total Score and a score for Pro-Social Behaviours. In addition, the Rutter scale has sub scores for a range of behaviours including: Hyperactivity [range = 0-6], Conduct Difficulties [range = 0-6] and Emotional Disturbances [range = 0-10]. With the exception of the Pro-Social Behaviour score, lower scores indicate better behaviour. The Rutter scale

Dental Attendance

Dental appointments were arranged via the local Community Dental Service clinic at one, three and six-months after GAdischarge.

Statistical analysis

Database preparation and analysis was conducted by the University Ofof Glasgow Department of Statistics. The behaviour at induction was tabulated by group. The Rutter Scale data were analysed using the R statistics package. Ssincludedemploying analysis of covariance, with linear models to examine the effects of further covariates.

ANCOVA was also used to assess the MCDAS-FIS scores. And significance was set at the 5% level.

The original power calculation was based on the estimated effect of Midazolam upon cognitive performance, and is reported elsewhere [10.]

Results

One-hundred-and-eighty-one subjects, aged 5 to 10 years (mean 6.53 years) were recruited. Two patients were removed from the analysis when their study codes were found to have been reversed leaving 179 subjects.. The CONSORT flow chart (Table 2) shows patient recruitment and throughput for the One subject, from the placebo group was found to have contact dermatitis immediately following the DGA visit. This was unrelated to the premedication but she was withdrawn from post-operative follow-up. .One subject did not receive a general anaesthetic following premedication. Table 3 showing demographic and clinical patient information confirms that the midazolam and placebo groups were well matched.

Dental Anxiety

One hundred and thirty-eight children (n=71 Midazolam) provided data pre-operatively and 48 hours after GA. Means (and standard deviations and ranges) were as follows. Pre-operative dental anxiety: Midazolam: 2.3, (0.78, 1.0 – 4.5) vs. placebo: 2.26 (0.78, 1.0 – 4.6). Post-operative dental anxiety: Midazolam: 2.4 (0.69, 1.29 – 4.5) vs. placebo: 2.52 (0.78, 1.0 – 4.4).

An ANCOVA was conducted to explore the difference in dental anxiety between Midazolam and placebo groups, with pre-operative scores used as a co-variant.   It was evident that many children had relatively low levels of pre-operative anxiety which would not be reduced further by Midazolam. Therefore, analysis was restricted to

children scoring high in pre-operative anxiety (MCDAS baseline score >2). These results demonstrateed that Midazolam pre-medication was then shown to be associated with a but statistically significant reduction in dental anxiety at 48 hours relative to placebo [estimated difference 0.31, standard error 0.12, p = 0.001].

Observed behaviour at anaesthetic induction

One hundred and seventy-eight children providedThere were data at anaesthetic induction. for 178 T. The here was missing data for one child regarding mask acceptance; for another the general anaesthetic was cancelled following the premed for reasons unrelated to the study. When the results were tabulated (Table 1) and as no observable differences were shown between the Midazolam and Placebo groups. Therefore no further statistical analysis was undertaken.

Pre and postoperative emotional and behavioural assessment

Revised Rutter Scale for School Age Children: A was conducted, using age as a covariateapplied toscores. There were complete data for 153 participants (Midazolam n=81, Placebo n=72).

Total Rutter Score: AT significant effect (p=0.048) effect was observedoverall effect whereby children of 8 years of age and over showed a slight decrease in Rutter total score (i.e. improvement) at one week compared to pre-operative baseline score: Midazolam (n=13) change from baseline –2.3 (5.3); Placebo (n=12) change from baseline –1.7 (6.6). There were no significant differences, however, as a function of premedication] .

Emotional and Conduct Rutter Subscales Scores: There were no significant changes from baseline to one week in either the emotional orconduct behaviours (p= 0.071 and p=0.214 respectively), and there was no effect of age.

Hyperactive Rutter Subscale Score: The midazolam and placebo groups both showed a significant, though clinically small, decrease in hyperactivity from the pre-operative to the one-week assessments: Midazolam p= 0.04, placebo p=0.02, pooled data p=0.002 [Midazolam baseline 2.03 (1.74), 1 week 1.68 (1.85); Placebo baseline 2.20 (1.61), 1 week 1.64 (1.84)]. However,, there were no significant differences between the treatment groups, nor was there a significant effect of age.

Prosocial Rutter Score: There was a significant improvement in pro social behaviours from pre-operative to week one assessments (p=0.002) [Midazolam baseline 15.5 (3.37), 1 week 16.51 (3.12); Placebo baseline 14.76 (4.04), 1 week 15.69 (3.25)], but, again, there were neither significant between-group differences nor any significant effect of age.

Dental attendance

Table 4 shows the parents' stated intention that their child would attend the Community Dental service for one, three and six-month follow-up compared to their actual attendance at the Clinic. No differences were observed between the groups.

Discussion

The present study shows that 0.2mg/kg of transmucosal Midazolam did not improve the child's behaviour at anaesthetic induction or reduce post-operative morbidity. However, midazolam pre-medication There was shown to reduce dental , however, a small but significant benefit in reducing anxiety in the most dentally anxious children. Whilst the

difference was statistically significant, it is unclear whether so small a change relative to placebo would have clinical significance.

The low dose of midazolam may be the reason for thisthese largely negative results, and further exacerbated by the fact that some of the midazolam might have been swallowed rather than absorbed transmucosally. The dose of 0.2mg/kg is lower than the normal oral dosage of 0.3mg/kg up to 1.0mg/kg. However, whilst a higher dose of midazolam might have exerted more beneficial effects [22], Ko Y P *et al* have shown 0.2mg/kg to be effective in reducing emergence agitation and post-operative analgesic requirements [23]. Moreover, Erlandsson *et al* have reported this dose to be effective for conscious sedation of unco-operative paediatric dental patients [24]. Nevertheless, Calipel et al. reported that even 0.5mg/kg oral Midazolam premedication was not an effective premedicant even when compared to non pharmacological approaches [25].

The authors had intended to administer a Midazolam dose of 0.3mg/kg but this was amended to 0.2mg/kg on the insistence of the ethics committee, whose rationale was to reduce the risks of respiratory depression and disinhibited behaviour, given the very short interval between anaesthesia and discharge in this type of ambulatory service. As such, any benefit to the child of a 0.3mg/kg dose for this ultra short procedure might have been outweighed by the known adverse cognitive side effects on discharge [26]. Interestingly, our cognitive function data confirmed significant short-term impairment even at this low dose [10].

The subjects in the present study reflect the type of child referred for dental extractions under general anaesthesia in Scotland in general and in this unit in particular [27, 28, 30]. Few recruits dropped out of the study and there was little missing data, and, surprisingly, only one child refused the premed – from the placebo group. On reflection, the results may have been influenced by the fact that both the RA and RN

were both women who were in constant, and emotionally supportive, contact with the child and parent throughout. This might have been an unwitting confounding factor that is, nevertheless, well recognised in the literature [29, 30]. Thus, thisthe supportive environment may in itself have achieved an effective level of preparation [31, 32], to which the low dose of midazolam might have had little further to add. A 'placebo-effect' was clearly evident in that almost half of the control group was observed to be drowsy, disorientated or asleep prior to anaesthetic induction.

Midazolam was shown to improve post-operative dental anxiety in most anxious children. It is possible that the reduction in post-operative anxiety may be attibuted to the amnesic effect of the drug. A previous controlled study, on the same population, confirmed that children self-reported significantly higher levels of dental anxiety post-operatively [6] and so, thisthe present finding is important. However, collecting self-reported child anxiety data using with the MCDAS was a challenge in the present study. The subjects were young and found to have littlethat, as prior knowledge of local analgesia and sedation, their comprehension parts of the MCDAS was poor. were. Moreover, it was necessary for us to compute new MCDAS threshold values denoting "anxiety"Whilstrevised thresholdof to denote 'anxiety'As a result, many participants failed to respond to all eight items and therefore an alternative method of analysing the scores was employed. Data was thus converted into mean scores and similar cut-off points for dental anxiety were determined using previously published literature (e.g. Wong et al.13). Whilst sound methods were used to translate the scores, as this is not yet validated,was derived in a logical way, our results should be interpreted with some caution.

For the sample as a whole, the behaviour of children appeared to improve after the DGA visit, with less hyperactivity and more positive engagement with their parents. The reason for such a positive behaviour change is unclear and it must be borne in mind

that these improvements were clinically small in that the magnitude of the improvement was less than 10%. The fact that post-operative emotional behaviour was better in the few children who were aged 8 years and above probably reflects their more advanced developmental level that confers greater understanding of the procedure and its effects, with consequent benefits to their coping. This result is also consistent with evidence of a negative relationship between children's age and disturbed behaviour and non-co-operation [33, 34] and crying and restless behaviour after general anaesthesia [35]. One might also speculate that, perhaps, the children felt better now that their toothache was alleviated; an alternative proposal might be that the children were concerned that if they misbehaved they would be sent for repeat treatment. It could also be possible that children were relieved that the GA process was behind them.

It could be argued that screening to exclude non-anxious subjects should have been performed prior to administration of a premedicant [36]. However, the children in this sample were <u>not</u> undergoing ordinary elective surgical procedures; instead they had been referred for this radical treatment on account of their poor dental condition, toothache and likely pre-existing dental anxiety [6, 37]. The fact that the population in the present study had pre-operative Total Rutter Scores approaching the previously validated indicator for *clinically significant disturbance* is evidence of their poor pre-operative behavioural and emotional state.

Despite parental agreement to continue to attend for dental follow-up the results in this regard were disappointing, though not surprising given the previous dental history and social deprivation scores of the sample. It is possible that some parents preferred to attend their general dental practitioner. However, it is common for children have lapsed registration following the DGA event.

Overall, this This randomised placebo-controlled trial in children undergoing general anaesthesia for dental extractions has shown that 0.2mg/kg Midazolam placed in the buccal pouch did not benefit dental anxiety generally, however the most dentally anxious children experienced a reduction in anxiety. Behaviour at anaesthetic induction, postoperative psychological morbidity and subsequent dental attendance were not found to differ between the pre-medication groups.

Table 1 Observed Behaviour at Anaesthetic Induction

Observed Behaviour (n=178)	Placebo	Midazolam
Child's willingness to sit on dental chair		
• Sits willingly on their own on dental chair	83	85
• Sits reluctantly on dental chair with some encouragement	4	2
• Sits on dental chair on parent's knee	1	2
• Parental physical restraint needed to hold patient on dental chair	1	0
• Child refuses to sit on dental chair	0	0
Rating for consciousness		
• Fully awake, alert	47	38
• Drowsy, disorientated	41	51
• Asleep	1	0
Rating for movement		
• Violent movement interrupting treatment	5	3
• Continuous movement making treatment difficult	4	5
• Controllable movement that does not interfere with treatment	18	18
• No movement	62	63
Rating for crying		
• Hysterical crying that demands attention	3	2
• Continuous, persistent crying that makes treatment difficult	6	4
• Intermittent, mild crying that does not interfere with treatment	9	9
• No crying	71	74
Child's mask acceptance*		
• Willingly accepts mask Accepts mask with some encouragement	78	79
• Refuses to accept mask	6	7
• Wants to hold mask themself	2	2
• Initially accepts mask but gets distressed during induction	2	0
	0	1
Rating for overall behaviour		
• **Aborted** – no treatment rendered	2	0
• **Poor** – treatment interrupted, only partial treatment complete	0	1
• **Fair** – treatment interrupted, but eventually all completed	3	3
• **Good** – difficult, but all treatment performed	6	7
• **Very good** – some limited crying or movement, e.g. during anaesthesia or mouth prop insertion	1860	11
• **Excellent** – no crying or movement		67

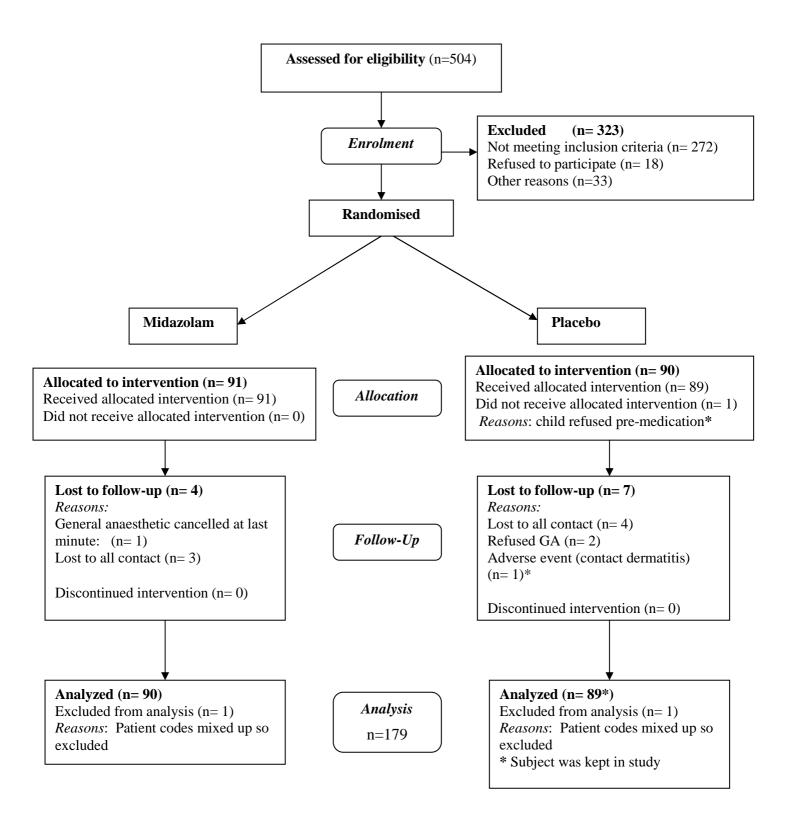***missing data on mask acceptance only: n=1**

Table 2. The Consort Flowchart

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                    ┌─────────────────────────────────────┐
                    │  Assessed for eligibility (n=504)    │
                    └─────────────────────────────────────┘
                                     │
                                     ▼
                            ┌──────────────────┐        ┌──────────────────────────────────────────┐
                            │   Enrolment      │───────▶│ Excluded        (n= 323)                 │
                            └──────────────────┘        │ Not meeting inclusion criteria (n= 272)  │
                                     │                  │ Refused to participate (n= 18)           │
                                     ▼                  │ Other reasons (n=33)                     │
                            ┌──────────────────┐        └──────────────────────────────────────────┘
                            │   Randomised     │
                            └──────────────────┘
                          /                        \
                         ▼                           ▼
            ┌──────────────────┐              ┌──────────────────┐
            │   Midazolam      │              │    Placebo       │
            └──────────────────┘              └──────────────────┘
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Allocated to intervention (n= 91)	*Allocation*	Allocated to intervention (n= 90)
Received allocated intervention (n= 91)		Received allocated intervention (n= 89)
Did not receive allocated intervention (n= 0)		Did not receive allocated intervention (n= 1)
		Reasons: child refused pre-medication *****

Lost to follow-up (n= 4)	*Follow-Up*	Lost to follow-up (n= 7)
Reasons:		*Reasons:*
General anaesthetic cancelled at last minute: (n= 1)		Lost to all contact (n= 4)
Lost to all contact (n= 3)		Refused GA (n= 2)
		Adverse event (contact dermatitis) (n= 1)*
Discontinued intervention (n= 0)		Discontinued intervention (n= 0)

Analyzed (n= 90)	*Analysis* n=179	Analyzed (n= 89*)
Excluded from analysis (n= 1)		Excluded from analysis (n= 1)
Reasons: Patient codes mixed up so excluded		*Reasons*: Patient codes mixed up so excluded
		* Subject was kept in study

Table 3. Demographic and clinical summary statistics

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Group	Midazolam (N = 90)	Placebo (N = 89)
Age: years (s.d.)	6.52 (1.36)	6.54 (1.38)
Sex: M/F	43/47	45/44
Social deprivation category		
1 - 2	3	4
3 - 5	32	28
6 – 7	55	57
Previous General anaesthesia		
None	70	66
Dental	11	12
Medical	6	10
Medical and Dental	3	1
Number of extractions		
2-5	28	32
6-10	52	44
11-16	10	12
Missing data	0	1

Table 4. Children's attendance at the Community Dental Service appointment

(a) One Month Dental Attendance

	Stated Intention to attend		Actual Attendance (having stated "Yes")	
	YES	NO	YES	NO
Midazolam: (n)	37	53	14	23
Placebo: (n)	26	63	5	21
	p = 0.13		p = 0.19	

_____

(b) Three Month Dental Attendance

	Stated Intention to attend		Actual Attendance (having stated "Yes")	
	YES	NO	YES	NO
Midazolam: (n)	36	54	15	21
Placebo: (n)	24	65	8	16
	p = 0.09		p = 0.70	

_____

(c) Six Month Dental Attendance

	Stated Intention to attend		Actual Attendance (having stated "Yes")	
	YES	NO	YES	NO
Midazolam: (n)	36	54	8	28
Placebo: (n)	23	66	6	17

$$p = 0.06 \qquad\qquad p = 0.98$$

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