TITLE: Randomised Study of the Use of Transdermal Buprenorphine vs. Codeine and Paracetamol as a Post-Tonsillectomy Analgesia in adults

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ABSTRACT

Objective: To compare the efficacy of Buprenorphine with transdermal administration 20 mcg/h to standard analgesics Codeine and Paracetamolin the management of post-tonsillectomy pain in adults.

The design was open label, Phase IV, prospective randomised controlled trial in adults consisting of 133 adults between 18-50 years of age.

The ain Outcome measures: were Perceived pain and drowsiness measured by Visual Analogue Scale (VAS), (2) Postoperative days requiring "rescue medication" (Diclofenac Sodium), and (3) Reported days of nausea.

Results: Random allocation to the intervention and control group achieved an adequate balance (31 intervention, 33 treatment as usual (TAU) and no significant demographic differences were found between the groups. The non-significant difference for the VAS Pain Scale (p = .082) favoured the intervention group. While with the VAS drowsiness scale, the non-significant difference (p = .853) also favoured the intervention group. There was no evidence suggesting either gender or age had effects on the outcomes. There was also no evidence to suggest that post-operative bleeding had an effect on VAS pain (p=.125) or drowsiness (p=.329), or for the haemostasis method (p=.586 for VAS pain and p=.561 VAS drowsiness).

Conclusions: Buprenorphine with transdermal administration has no significant advantage to the control of perceived post-tonsillectomy pain in adults. The lack of advantageous effect is consistent with reported drowsiness. The proportion of days participants took rescue medication was similar in both arms of the trials up to day 7. In the last 3 days of the 10 day period, the rescue medication taken was higher in the control group.

key words- tonsillectomy, pain, analgesia, post operative, transdermal, buprenorphine,

INTRODUCTION

Background

Tonsillectomy is a commonly practiced surgical procedure in both adults and children, with 50,531 procedures performed in the United Kingdom in 2003/2004.[1] While patients often have an improved quality of life following surgery, there can be cause severe pain in the immediate post-operative period.[2] The resultant odynophagia from surgery can lead to decreased oral intake, dehydration, infection and secondary haemorrhage.[3] It also can affect analgesic consumption, length of inpatient stay, and return to regular function.[4]

Post tonsillectomy pain, referred otalgia and painful swallowing are often common symptoms, and are caused by inflammation and its mediators, breach of mucosa, nerve irritation, and spasm of the exposed muscles.[5] Pain can last for 10 days or longer, and is related to the systemic inflammatory responses following surgery. In adults, the pain can be very intense affecting rehabilitation. In addition, post-operative vomiting is a common symptom, and can further complicate the administration and effectiveness of oral analgesics.[6]

An alternative to the standard oral intake of pain medication would be to deliver the analgesic buprenorphine through a transdermal patch. Buprenorphine is a derivative of thebaine, a semi synthetic potent analgesic, and is used for the treatment of moderate-to-severe pain. Sittl suggests that it has an antinociceptive potency between 75 to 100 times greater than that of morphine.[7] It can be administered through a number of different routes including epidural, intrathecal, intramuscular,sublingual,transdermal, and intra-articular, enabling control of pain in the post-operative period.[8] Budd and Collett suggest that sublingual Buprenorphine is a particularly effective breakthrough agent, and can be used effectively against the symptoms of chronic pain, with minimal side effects.[9, 10]

Objectives

The aim of this study is test the effectiveness, through reported levels of pain, nausea, and drowsiness, of the analgesic buprenorphine 20 mg (20μg/h BuTrans) using a matrix transdermal patch in comparison with standard post tonsillectomy pain management in patients between 18-50 years used in current clinical practice i.e. Paracetamol 500mg; codeine phosphate hemihydrate 30 mg (Solpadol effervescent tablets).

METHODS

Ethical considerations

This is a prospective randomised controlled open label trial in adults approved by the regional ethics committee. The study medication was in accordance with the Medicines and Health Care Products Regulatory Authority (MHRA) approved protocol and under the sanction of a clinical trial authorisation.

Participants

The study took place in Ysbyty Gwynedd Hospital, Bangor, North West Wales. Recruitment started on15/11/2007 and study ended on 15/02/2012. Patients undergoing tonsillectomy, aged 18 to 50 years old, who met the American Society of Anaesthesiologists (ASA) grade I & II criteria, were recruited in the trial.

Patients were excluded with conditions in which the respiratory centre function was severely impaired; patients with asthma and/or allergic to non-steroidal anti-inflammatory drugs; hypotension; pregnancy and lactation; recent head injury; known hypersensitivity towards the active substance or to any of the excipients; opioid-dependent patients and/or in narcotic withdrawal treatment; patients who were receiving monoamine oxidase (MAO) inhibitors or had taken them within the last two weeks; patients suffering from myasthenia gravis; patients suffering from delirium tremens or acute alcohol intoxication or convulsive disorders. Patients were admitted to the hospital through the day surgery unit or inpatient ward. Eligible patients were given verbal and written explanation about the trial in advance and written, informed consent was obtained.

Surgical techniques and post-operative instructions

The designated ENT surgeons performed the tonsillectomy by their method of choice, either hot or cold dissection. Haemostasis was achieved by silk ties, bipolar forceps or monopolar forceps. It is acknowledged that the level of post tonsillectomy pain varies with surgical technique and therefore this variable will be accounted for in the analysis.

In the i postoperative phase, patients in both groups received standardised analgesic medication; s morphine 10 mg (4 hourly), oral diclofenac 50 mg (8 hourly),co-codamol 30/500 (Solpadol) x (2 tablets 4 hourly with a maximum of 8 tablets in 24 hours), and cyclizine 50 mg (6 hourly as and when needed) whilst in hospital.

For patients in the intervention group (Patch), a buprenorphine 20 mg (20 µg/h BuTrans) 7 day transdermal patch was applied on arrival to the ward from theatre recovery. The intervention group received additional cyclizine hydrochloride for nausea. The treatment as usual (TAU) group received a 7 day supply of codeine phosphate 30 mg/ paracetamol 500 mg on discharge. Patients in both groups received a 10 day supply of rescue medication consisting of diclofenac sodium dispersible tablets.

Patients were issued an event diary for daily recording of medication taken (including rescue medication), the perceived pain (recorded on the Visual Analogue Scale)[11] and the Pain Coping Strategies Questionnaire.[12] On discharge, patients were advised to comply with the medication protocol, accurately record any rescue medication taken, post tonsillectomy haemorrhage, vomiting and readmission to the hospital. Ten days following tonsillectomy, patients were invited to the postoperative clinic to discuss progress, enquire about pain control, and return the booklet. Patients who were unable to attend the clinic were given a self-addressed envelope, and those who did not return the diary were contacted by telephone.

Objectives

The aim of this study is test the effectiveness of an analgesic buprenorphine 20 mg (20 µg/hour BuTrans)

matrix transdermal patch in comparison with standard post tonsillectomy pain management in patients between 18-50 years is used in current clinical practice i.e. paracetamol 5OO.Omg;codeine phosphate hemihydrate 30.0mg (Solpadol effervescent tablets).

Outcomes

The primary objective was to assess the efficacy of the patch compared to TAU as measured by the VAS pain. The secondary outcomes were VAS drowsiness, and the number of days that rescue medication was used, or the patient felt sick. The effect of tonsillectomy method and post-operative haemorrhage on VAS pain would also be assessed.

Sample Size

Initially the study was intended to recruit 150 participants in each arm of the study. This would have been a sufficient number to give an effect size of 0.3 significance at the 5% level, with 80% power for the analysis of the primary outcome. However, given the difficulties of acquiring completed diaries and the poor retention of participants, we decided to stop the study after 138 patients had been recruited. This would give an effect size of 0.5 significance at the 5% level with 80% power.

Randomisation

Allocation to the intervention group or TAU (treatment as usual) was done by simple (non-stratified) randomisation. The randomisation was performed by the R&D office (independently from the research team) using a web-based random numbers table generator.[13]

The Data Collection form was completed by the Chief investigator using the surgeon's notes and included the details of the operation technique and the method of haemostasis. Post-tonsillectomy haemorrhage, vomiting, rescue medication use, and readmission incidence were also recorded in the Data Collection Form from the patient diary or entries in the patient's medical record

Statistical methods

We report here the visual analogue scale (VAS) for perceived pain and drowsiness. Also reported are whether or not rescue medication was used and whether or not the patient felt sick. These four measurements were recorded daily for ten days by the patient in a diary.

The analysis was by treatment as allocated. Using the trapezoidal rule, we estimated the area under the curve (AUC) for the VAS pain and VAS drowsiness. Differences in treatment arms for the AUC outcomes were assessed by a regression analysis and by logistic regression for the number of days out of ten that rescue medication was used or the patient felt sick. The analyses were adjusted by age, gender and coping strategy. The effects of tonsillectomy method and post-operative haemorrhage were assessed by inclusion as factors in the above models.

For the primary outcome, missing values on the VAS scales at the end of the ten day period when the two

previous values were both small (<20) were replaced by '0', while linear interpolation was used to estimate missing values in the middle of the ten day period; otherwise the AUC was set to missing. To assess the impact of all missing data we imputed the AUC and the proportion of days rescue medication was taken and nausea reported using five multiple imputations[14]and compared it to the main analysis.

Coping strategy was derived from the coping strategies questionnaire (CSQ).[12]Three factors can be derived from the questionnaire which assess; (1) Cognitive coping and suppression, (2) Helplessness, and (3) Diverting attention and praying/hoping. These three factors were included in the regression analyses as extra covariates.

RESULTS

Demographics and clinical characteristics

From the 138 randomised participants, a total of 64 (46%) returned the diaries. Of these, 53 (83%) had complete data for the VAS pain, 48 (75%) for VAS drowsiness, 44 (96%) for rescue medication and 34 (53%) for reported nausea. The frequency of missing responses for each outcome measure is illustrated in Table 1 which shows data was better reported by the TAU group.

The demographic and clinical characteristics for the 64 participants who returned the questionnaires are shown in Table 2 which shows there were no important differences in the composition of the treatment arms. The trajectory of the unadjusted mean scores for perceived pain and drowsiness are illustrated in Figures 1 and 2 respectively.

Clinical effectiveness

For the main analysis, individual measurements on VAS pain were estimated for 2 (3%) participants and 9 (14%) for VAS drowsiness using the methods articulated in the previous section. This left a total of 9 (14%) participants for VAS pain and 7 (11%) for VAS drowsiness with missing AUC values which were imputed for the sensitivity analysis.

The main analysis summarised in Table 3 reveals a non-significant difference for perceived pain ($F(1, 53) = 2.87$, $p = .096$) in favour of the Patch group with no covariates included in the regression model. When age and gender were included in the model neither covariate was significant ($F(1, 51) = 0.47$, $p = .497$) for age and ($F(1, 51) = 0.05$, $p = .819$ for gender), and the effect still favoured the Patch group but was again not significant ($F(1, 51) = 3.14$, $p = .082$). When age, gender and the three CSQ factors were included there was a significant effect favouring the Patch group ($F(1, 35) = 5.35$, $p = .027$). A forward regression analysis found that only the CSQ factor for cognitive coping and suppression was significant ($F(1, 39) = 12.26$, $p = .001$), and again found a significant effect favouring the Patch group ($F(1, 39) = 5.00$, $p = .031$). However the sensitivity analysis did not confirm the findings of a difference between the treatment groups for any of the analyses.

No significant differences between treatment groups were found for perceived drowsiness (p=.853) also

favouring the Patch group. Age and gender were not significant covariates. Full results are shown in table 3. Results of the exploratory analysis showed the method used to remove the tonsils had no effect on perceived pain ($F(2, 48) = 0.59$, $p = .586$) or drowsiness ($F(2, 50) = 0.56$, $p=.561$). Post-operative haemorrhage had no effect on pain ($F(1, 48) = .13$, $p= .125$) or drowsiness ($F(1, 50) = 0.33$, $p= .329$).

There was no significant difference in the proportion of days participants reported taking rescue medication between the two treatment groups (OR= 0.76, 95%Cl = 0.48 to 1.19, $p = .227$). No significant difference between groups was found either in the proportion of days participants felt sick (OR = 0.47, 95%Cl = 0.21 to 1.05, $p = .062$).

DISCUSSION

Post-tonsillectomy pain is rather unpleasant, and despite improvements in surgical and anaesthetic techniques improving postoperative morbidity, it has a significant impact on the quality of life of the patient. Postoperative pain after tonsillectomy appears immediately following the operation and increases in intensity until between the third and fifth postoperative day, and this was also observed in our findings.[15, 16, 17] A wide variety of pharmacological agents have been used post-tonsillectomy with conflicting results, as the pain reliever must not increase bleeding and must have minimal side effects.

Our results unfortunately did not suggest any significant difference in the reported levels of pain, drowsiness, nausea, or days taking the rescue drug between the Patch group and TAU group. However, the Patch delivery of buprenorphine may give patients a greater sense of control over their pain, and give a better, more controlled delivery of the analgesia. Certainly, some studies have shown that patients, particularly children, post-tonsillectomy, do not take adequate amounts of analgesia, particularly during the night, and despite the pain reported.[18] This may be exacerbated by inflammation and pain of the throat, vomiting, and inadequate levels of water intake.

A number of studies examining post-tonsillectomy pain management have found no significant change in the levels of reported pain by patients using a range of different analgesics. For instance, Mikkelsen and colleagues, in a randomised study of rofecoxib plus gabapentin vs. rofecoxib plus placebo concluded that although gabapentin reduced the opioid requirement in first 24 hours after tonsillectomy, found no statistical difference from days 2-5.[19] While Naesh and colleagues in a randomised controlled trial of rofecoxib and paracetamol vs. placebo and paracetamol concluded no overall difference in pain scores during the first 24 hours.[20]

However, the studies above have tended to evaluate pain control using an indication of the perceived pain measured by Visual Analogue Scale. Vaimanand colleagues conducted a complex evaluation of pain after tonsillectomy in 50 randomly chosen adults, and noted that signs of clinical recovery after tonsillectomy did not always correspond with VAS pain score.[21] This has been reinforced by findings from other studies looking at the clinical benefits of adequate pain control, [16] and may indicate a subjective role of the perceived pain of

patients. Examining different forms of pain management may lead to benefits in the control patients feel over their pain, leading to a better experience and recovery. A systematic review of postoperative pain and the use of analgesics by Ip and colleagues found in their examination of coping strategies that patient's pre-existing pain, age, type of surgery, and anxiety influences reported pain.[22] In our study, we found that a relationship between the results of the cognitive coping of patients and the reported effectiveness of pain control for the treatment, which may reflect the increased level of control patients feel when using this treatment.

Study strength and weaknesses of the study

The study was designed as an open label randomised controlled trial. We acknowledge that a blind trial would have been methodologically preferable but the nature of the comparison (transdermal patch vs. effervescent tablets) made the blinding of participants impossible, and we encountered logistical challenges in sourcing placebo patches/effervescent tablets. Similarly, a patch vs. placebo controlled trial was deemed unethical, as a clinically effective comparator exists and is used in routine clinical practice. However, the study was analysed blind.

A major weakness of the study was the number of participants who did not complete the study, with, 54% lost to follow-up or who did not complete the trial, compared to the 40% estimated at the beginning of the trial, and despite 133 patients remaining, less than half of these completed and returned their questionnaires. We obtained ethical approval and patient consent to remind participants to return the questionnaires, but found that diaries obtained following the reminder no longer recorded accurately the daily scores of pain and rescue medication taken. There was no difference in the number of drop-outs between the intervention group and the TAU group, between those withdrawing from the trial, or those completing the trial. It is difficult to determine the reasons for this as we were unable to contact participants to make further assessments.

A possible solution to this issue may have been to have required follow-up sessions at a pre-determined intervals, which would have recorded the amount of remaining medication and ensured the completion of questionnaires at those time points, or daily telephone check-ups, which would have captured the needed outcome measures. However, this would have required substantial resources, which were not available during the study. Furthermore, it would have been useful to have included a telephone exit interview in the protocol; this would have given some data and insight into the possible reasons for participants not completing the study, although participants may not have wished to complete this.

The study did not include a substantial review of the health economic benefits or costs of the treatment, although a superficial examination found no significant difference in the administering cost of transdermal buprenorphine over the TAU.

Conclusions

Inadequate analgesia post-tonsillectomy is a significant problem in terms of the subjective pain perceived by the participant, as well as being a hindrance to their clinical recovery. Our study suggests that providing patients with a buprenorphine transdermal patch is an alternative method of post-operative pain control following tonsillectomy in adults, but yields no better pain control than treatment as usual. Sustained pain control by transdermal delivery of buprenorphine has an added advantage over the orally administered medication. Unfortunately, the study was underpowered, due to a larger than expected drop-out rate, and wasn't able to demonstrate this with any degree of statistical significance. Furthermore, we were unable to determine the reasons for this; it may be that with effective pain management participants are no longer motivated to record or monitor their symptoms, or participants feel disengaged from the study once discharged. Future research into this area should develop strategies to ensure and monitor patient involvement, and examine why patients do not complete trials.

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Figure 1: Unadjusted means of VAS pain scores over time by treatment arm

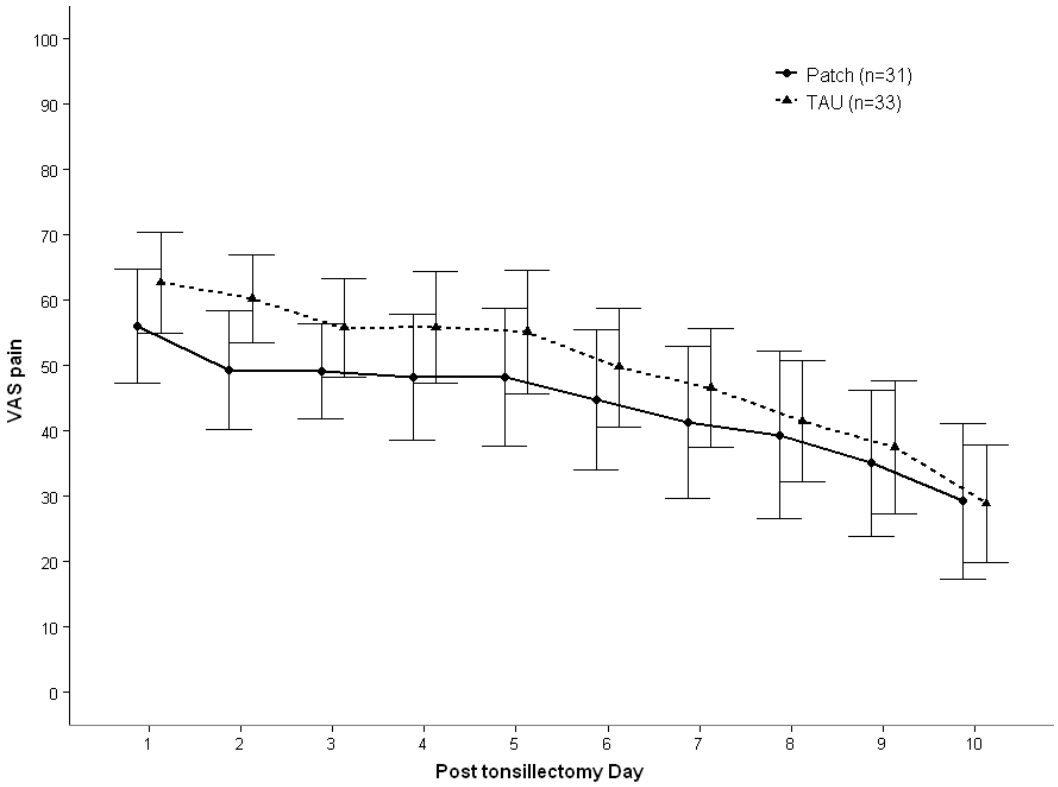


Figure 2: Unadjusted means of VAS drowsiness scores over time by treatment arm

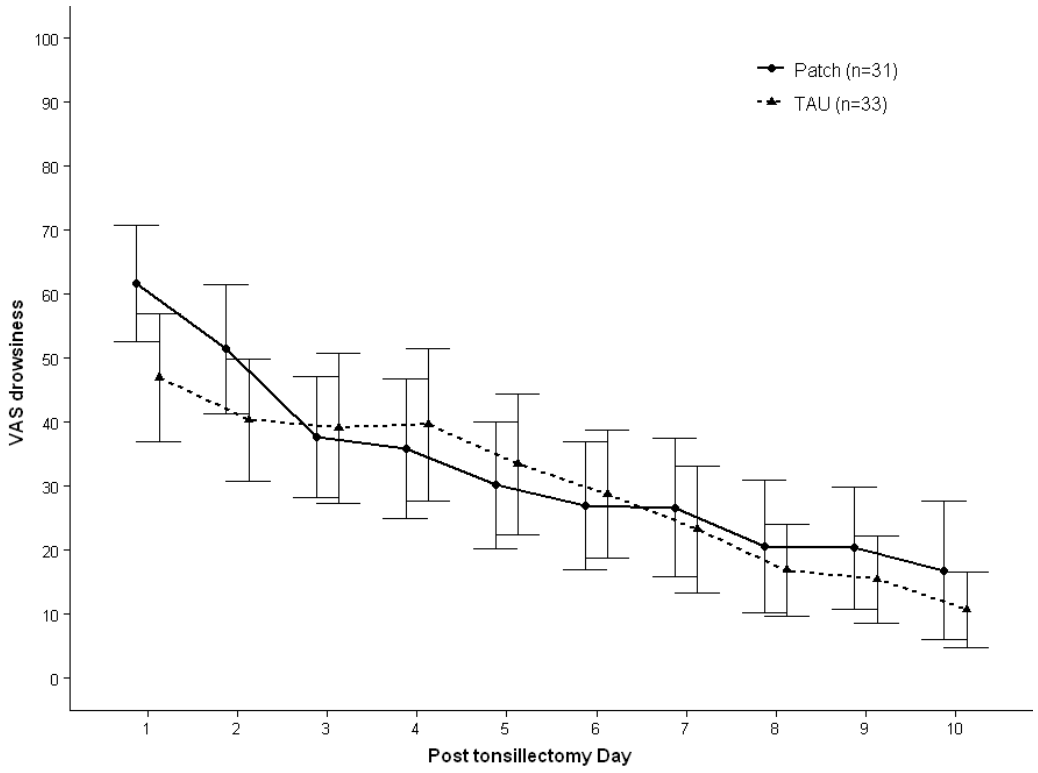


Table 1

Frequency of missing responses for Patch (N = 31) and TAU (N = 33).

	VAS pain		VAS drowsiness		Rescue medication		Nausea	
	Patch	TAU[t]	Patch	TAU	Patch	TAU	Patch	TAU
Day								
1	0	0	0	0	1	0	3	1
2	0	0	0	0	3	0	4	2
3	2	0	3	1	3	1	7	1
4	4	0	5	1	7	1	7	2
5	5	0	5	3	8	1	9	2
6	6	0	7	0	8	0	7	0
7	6	0	7	0	10	2	10	3
8	9	0	9	0	14	1	13	5
9	10	0	10	0	13	1	0	5
10	11	0	11	0	15	1	0	4
Total	53	0	57	5	82	8	60	25

[t] - Treatment as usual

Table 2

Demographics and clinical characteristics of the participants by treatment allocated

		Patch	TAU[t]
Age	Range	18-41	18-43
	Mean (SD)	26 (8)	26 (7)
Gender,n (%)	Male	13 (42)	9 (27)
	Female	18 (58)	24 (73)
Chronic Tonsillitis, n (%)		29 (94)	33 (100)
Peritonsillar abscess, n (%)		2 (6)	
Tonsillectomy method,n (%)	Dissection	24 (77)	20(61)
	Bipolar	5 (16)	11 (33)
	Monopolar	2 (6)	2 (6)
Haemostasis method, n (%)	Ties	4 (13)	9 (27)
	Ties + bipolar	20 (65)	11 (33)
	Monopolar	2 (6)	2 (6)
Post-operative haemorrhage, n (%)	No	30 (97)	30 (91)
	Yes	1 (3)	3 (9)
Incidents,n (%)	No	28 (90)	30(91)
	Yes	3 (10)	3 (9)
CSQ factors			
Cognitive coping and suppression	Range, n	0-3.94, 22	0.33-4.78, 29
	Mean (SD)	1.99 (1.21)	2.34 (1.18)
Helplessness	Range, n	1.50-4.33, 26	0.25-4.29, 28
	Mean (SD)	2.86 (0.71)	2.65 (0.78)
Diverting attention and praying/hoping	Range, n	0-3.58, 24	0.33-4.08, 29
	Mean (SD)	1.87 (1.02)	2.22 (0.87)

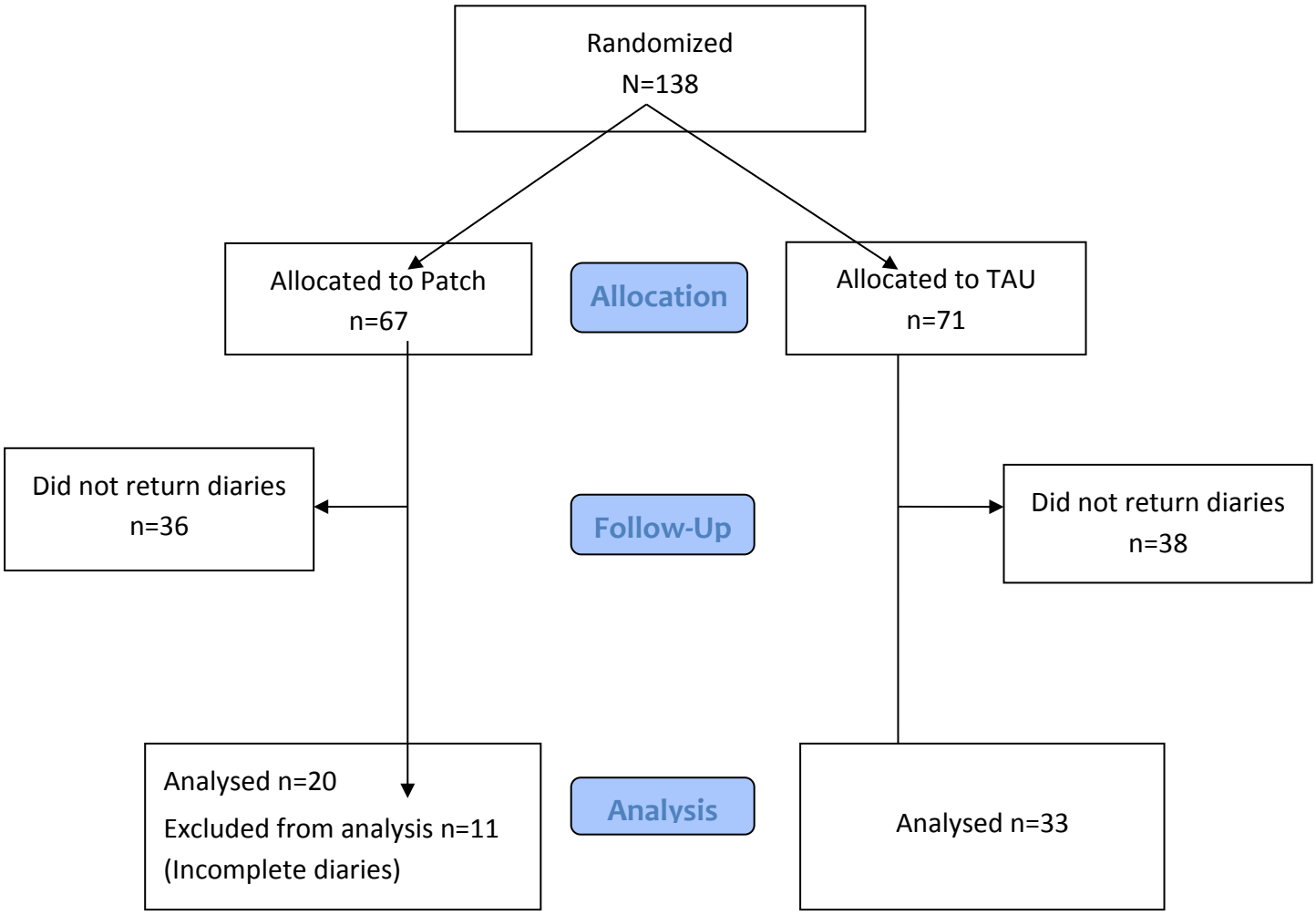
[t] - Treatment as usual

Table 3

Difference (TAU – Patch) in Area under curve (defined over a 10 day period) of VAS pain and drowsiness adjusted for covariates.

	Original data			Pooled imputations		
	mean	SD	p	mean	SD	p
AUC VAS pain						
no covariates	8.40	4.96	0.096	7.39	5.23	0.162
Age , Gender	9.21	5.20	0.082	7.73	5.41	0.158
Age, Gender, 3 CSQ factors	13.28	5.74	0.027	10.65	6.20	0.101
CSQ (cognitive coping and suppression)	11.41	4.77	0.021	9.57	5.65	0.104
AUC VAS drowsiness						
no covariates	1.79	4.82	0.712	-0.01	4.86	0.998
Age , Gender	1.70	4.91	0.731	-0.15	4.88	0.976
Age, Gender, 3 CSQ factors	5.63	5.02	0.270	1.04	4.96	0.834
CSQ (cognitive coping and suppression)	5.42	4.44	0.229	1.31	4.66	0.780

CONSORT Flow Diagram



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5,8
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			

Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how 8	6
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5,6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	5
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	4(Table 2)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13,14 (table 2 and 3)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	7,8

Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14(table 2)
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	9
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	ISRCTN
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.