Psychological Medicine

cambridge.org/psm

Original Article

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Cite this article: Dib JE *et al*. (2022). Rapid tranquillisation in a psychiatric emergency hospital in Lebanon: TREC-Lebanon – a pragmatic randomised controlled trial of intramuscular haloperidol and promethazine *v.* intramuscular haloperidol, promethazine and chlorpromazine. *Psychological Medicine* **52**, 2751–2759. https://doi.org/10.1017/S0033291720004869

Received: 23 June 2020
Revised: 18 November 2020
Accepted: 23 November 2020
First published online: 6 January 2021

Key words:
Rapid tranquillisation; randomised clinical trial; TREC; intramuscular; lebanon

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Rapid tranquillisation in a psychiatric emergency hospital in Lebanon: TREC-Lebanon – a pragmatic randomised controlled trial of intramuscular haloperidol and promethazine *v.* intramuscular haloperidol, promethazine and chlorpromazine

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Abstract

Background. Agitated patients constitute 10% of all emergency psychiatric treatment. Management guidelines, the preferred treatment of clinicians differ in opinion and practice. In Lebanon, the use of the triple therapy haloperidol plus promethazine plus chlorpromazine (HPC) is frequently used but no studies involving this combination exists.

Method. A pragmatic randomised open trial (September 2018–July 2019) in the Lebanese Psychiatric Hospital of the Cross in Beirut Lebanon involving 100 people requiring urgent intramuscular sedation due to aggressive behaviour were given intramuscular chlorpromazine 100 mg plus haloperidol 5 mg plus promethazine 25 mg (HPC) or intramuscular haloperidol 5 mg plus promethazine 25 mg

Results. Primary outcome data were available for 94 (94%) people. People allocated to the haloperidol plus promethazine (HP) group showed no clear difference at 20 min compared with patients allocated to the HPC group [relative risk (RR) 0.84, 95% confidence interval (CI) 0.47–1.50].

Conclusions. Neither intervention consistently impacted the outcome of 'calm', or 'asleep' and had no discernible effect on the use of restraints, use of additional drugs or recurrence. If clinicians are faced with uncertainty on which of the two intervention combinations to use, the simpler HP is much more widely tested and the addition of chlorpromazine adds no clear benefit with a risk of additional adverse effects.

Introduction

Background

Aggression is the observable progressive behaviour (Anderson & Bushman, 2002; Dollard, Miller, Doob, Mowrer, & Sears, 1939) with the goal of causing harm whether physical or psychological towards another organism or object – while the person is motivated to escape, diminish or avoid such an action (Berkowitz, 1989; Dodge, Pepler, & Rubin, 1991); Vitiello & Stoff, 1997). It arises in 10% of all psychiatric emergencies mainly as a consequence of psychiatric disorders (Volz, Khorsand, Gillies, & Leucht, 2007). To undertake a diagnostic history and physical tests and before drug regimen begins, guidelines recommend that the patient must be calm and have some degree of co-operation (National Institute of Clinical Excellence, 2015). However, the risk presented often makes this difficult and sometimes impossible. When prevention and

de-escalation fail, to ensure the safety of everyone involved, rapid tranquilisation (RT) may be unavoidable.

Methods of RT vary – ranging from verbal, physical and pharmacological interventions (Brophy, Roper, Hamilton, Tellez, & McSherry, 2016; National Collaborating Centre for Mental Health, 2015; Ryan & Bowers, 2005) and what actually happens in front-line care varies (Cannon, Sprivulis, & McCarthy, 2001; Cooper, Browne, McClean, & King, 1983; Haw, Stubbs, & Gibbon, 2013; Huf et al., 2002; Lepping, 2013; Moritz, Jenvrin, Canivet, & Gerault, 2004; Pilowsky, Ring, Shine, Battersby, & Lader, 1992;Paton et al., 2019) and may even differ from what the local clinicians recommend (Bervoets et al., 2015; Binder & McNiel, 1999; Cunnane, 1994; Reid & Hughson, 2003). Preliminary to this trial we investigated the situation in Beirut and here too clinicians' opinions differ in some ways to the detail what happens in practice (Dib et al., 2018). The Lebanese survey (Dib et al., 2018) highlighted similarities of RT practices to what occurs worldwide (Migon et al., 2008) – such as the use of restraints (in this case straitjackets) that are administered by trained health-care professionals to prevent aggressive patients from hurting themselves and others (Chanine & Chemali, 2009). However, the Lebanese survey highlighted that the triple therapy of haloperidol plus promethazine plus chlorpromazine (HPC) was the standard emergency treatment of choice (Dib et al., 2018) (Table A1 in Appendix).

The triple therapy, although used elsewhere (Huf, Coutinho, & Adams, 2007) had never been tested within a randomised trial. Other RT treatments used in Beirut had, however, been trialed – most notably the haloperidol plus promethazine (HP) combination (Huf, Alexander, Gandhi, & Allen, 2016). Clinical trials within the Middle East are rare and randomised controlled trials in the psychiatric emergency setting are virtually non-existent (Nair, Ibrahim, & Celentano, 2013). The Lebanon-UK team felt this to be an opportunity to undertake a pragmatic trial, designed in Beirut, of practice used locally and providing outcomes of relevant to routine practice. Post survey and after a process of local consultation, the protocol for TREC[†1]-Lebanon was developed (Dib et al., 2019) and registered (Clinical Trials.gov, 2018).

Aim

To compare the triple therapy (HPC) with the well-researched HP combination for managing aggression in the Lebanese psychiatric setting within the context of a pragmatic randomised trial.

Methods

Like past TREC trials (Alexander et al., 2004; Huf et al., 2007; Raveendran, Tharyan, Alexander, & Adams, 2007; TREC Collaborative Group, 2003), the design of this study aimed to be simple and efficient – and not to interfere with routine practice. The design, including eligibility criteria and outcome measures, were informed by both local consultations, consideration of past work and our survey of practice in Lebanon (Dib et al., 2018).

Setting

This trial was conducted in Beirut, Lebanon (Population approximately 6 million), in a single public psychiatric hospital (Psychiatric Hospital of the Cross) – the largest inpatient psychiatric hospital in the country. This hospital has around 950 beds providing acute and long-term care for patients of all ages with mental disorders, including psychiatric illnesses and intellectual disabilities. The hospital does not have a clear policy on restraints yet maintains the highest integrity of ensuring patient safety with restraints only being used if the patient presents an extremely aggressive state of causing intense harm (i.e. physical violence) to others as well as oneself (Chanine & Chemali, 2009).

Patient selection

Patients were eligible if, having arrived at the psychiatric hospital, they clearly needed acute intramuscular sedation because of aggression, agitation or violence, if they were aged between 18 and 65, not already a participant in TREC-Lebanon, and the attending clinician was not already committed to the use of the double (HP) or triple therapy (HPC) for this particular person. Patients were ineligible if either of the interventions were thought to pose an additional risk for the patient.

Consent procedures

From our survey (Dib et al., 2018), we expected most potentially eligible patients to be accompanied by family members. This was, indeed, the case in the trial. The remaining patients were brought in by friends or officers of the law (Dib et al., 2018). When relatives were present and the potential trial participant clearly lacked capacity (Dib et al., 2019), the clinician used a consent sheet and direct interview to inform relatives of the nature of the trial, its risks and benefits and their right to withdraw their relative for whatever reason without detriment to their care. If relatives were not present and the patient clearly lacked capacity yet needed treatment that could not be delayed, this patient was entered into the trial. Upon reaching a state of calm, this person was then talked through and given a consent form explaining the study and their right to withdraw their details for whatever reason they saw fit without any effect on their care.

Intervention

The Psychiatric Hospital of the Cross, Beirut has standardised the doses of the three drugs involved (haloperidol 5 mg; promethazine 25 mg; chlorpromazine 100 mg). We compared HP with the triple therapy HPC. The double or triple therapy was administered as one intramuscular injection – the drugs being drawn into the same syringe. Although there is the standardisation of doses, the attending physician was free to change these if she/he felt that was indicated. All subsequent treatments were completely the discretion of the doctor or nurse.

Randomisation and allocation concealment

Randomisation was computer-generated and undertaken in the UK (by CEA) using a free online programme (https://www.randomizer.org/). The computer-generated randomly ordered, randomly sized small blocks, stratified by male and female. The codes were then sent to a person working at the hospital who played no role in admission of patients and created TREC-envelopes (fully opaque, identical in appearance and weight, numbered, consecutively ordered, A4 size, containing A6 notes naming the intervention of allocation) – 70 for men, 30 for women – the ratio predicted by

†The notes appear after the main text.

https://doi.org/10.1017/S0033291720004869 Published online by Cambridge University Press

our survey (Dib et al., 2018). On the outside of the A4 envelope was the TREC-Lebanon entry form. This was completed by the doctor *before opening the envelope*, who was at that point 'blind' to the intervention within the envelope. Once the envelope was open the trial was not blind.

Statistical methods and sample size

In such a situation, even a small advantage for an intervention could represent a worthwhile benefit. A set of sample size calculations were originally undertaken for a 15% difference in the primary outcome (proportion calm/tranquilised by 20 min) for a sample size of 100–150 participants (Table 1).

Table 1. Sample size needed to detect an absolute difference of 15% in the proportion of tranquillised patients ($\alpha = 5\%$, power = 80%)

HP	HPC	Projected *N*
% tranquilised		
5	20	**152**
10	25	**200**
15	30	**242**
20	35	**276**
25	40	**304**
30	45	**326**
35	50	**340**

Procedures

Once an aggressive patient requiring RT was eligible for randomisation, if possible, the resident clinician sought consent from relatives and, if granted, filled out the TREC-Lebanon entry form printed onto the *next consecutive* TREC envelope (trial entry). Only participating medical residents could randomise eligible participants.

For patients who were eligible but did not have an accompanying relative, trial entry proceeded and seeking of consent deferred until the person recovered. The entry form recorded demographic characteristics, suspected cause of the aggression, its severity (Busner & Targum, 2007) and the attending doctor's name. Upon completing the entry form, the resident opened the envelope and, thereafter, was no longer blind to the allocated treatment. The envelope contained the intervention note detailing HP or HPC and outcome forms including a free-text serious adverse event form. The clinicians were free to give the treatment suggested by the note in the envelope – at doses chosen by them – or to deviate from that. Once the intervention was administered, the resident started a phone timer set to ring at 20, 40, 60 and 120 min and then recorded simple outcomes (whether the person was calm/tranquil or asleep) at these times. JD retrieved all other information from case files.

Outcomes

Primary: calm or tranquil at 20 min (true primary outcome) and then at 40, 60 and 120 min.

Secondary: asleep, restrained/straightjacket applied, left the ward (at 20, 40, 60 and 120 min), recurrence of index aggression (defined as a recurring episode within the 20, 40, 60 and 120 min time intervals), new aggressive event (defined as a new aggressive episode beyond the 120 min time interval), medications used, serious adverse event (defined as a serious adverse event from the time of intervention to 2 h) and discharged (at 2 weeks).

All outcomes were recorded unblinded to the treatment of allocation.

Patients who were asleep were mutually noted as calm and tranquil and, as per hospital policy, if sleeping, people were no longer restrained. However, it was possible for people to be still restrained if calm or tranquil – but not more than 20–40 min.

Ethics, data and safety monitoring

As TREC-Lebanon was a joint collaboration between the University of Nottingham (UK) and the Psychiatric Hospital of the Cross (Lebanon), ethics approval was obtained from both institutional bodies – the University of Nottingham's Division of Psychiatry and Applied Psychology Ethics Board and the Psychiatric Hospital of the Cross Ethics Committee. An independent Data Monitoring Committee was recruited and informed on the trial's progress monthly – or should a serious event have occurred. This committee had a responsibility to inform a Steering Group of any untoward events and presented tabulated data to the Steering Group at 6 months.

Analysis

We assessed randomisation by comparing sociodemographic and clinical characteristics between the two treatment groups and calculated relative risks (RR) and number needed to treat [with 95% confidence intervals (CI)] for primary and secondary outcomes using intention to treat analysis. We calculated and interpreted CI for numbers needed to treat according to Altman (Altman, 1998). We evaluated statistical significance at the 5% level for the primary outcome and at 1% for secondary outcomes. We used κ statistics for estimating the inter-rater agreement for the primary outcome. Data were entered and analysed using SPSS 25 (IBM Corp, 2017) and RevMan 5.3 (Review Manager, 2014)

Results

Characteristics of patients at trial entry

Across the 10-month period of recruitment (September 2018–July 2019) we recruited and randomised 100 participants that met the criteria for eligibility. All participants were randomised in order.

Around 134 eligible participants were not included as they were admitted into the hospital during late night hours and residents on night duty were not part of the trial out of personal choice.

We know that 40 of the aggressive people who presented fell outside the age range of this study (were under 18 or over 65). Of the remaining 104 who did not enter the trial nearly half could not progress as their insurance did not cover the care in the hospital. The remainder either arrived already medicated, or the doctor felt that a specific treatment was indicated or a simple omission occurred. One hundred people were randomised (See Fig. 1).

Patients in both intervention groups had similar baseline characteristics and presumed cause of agitation (Table 2) indicating

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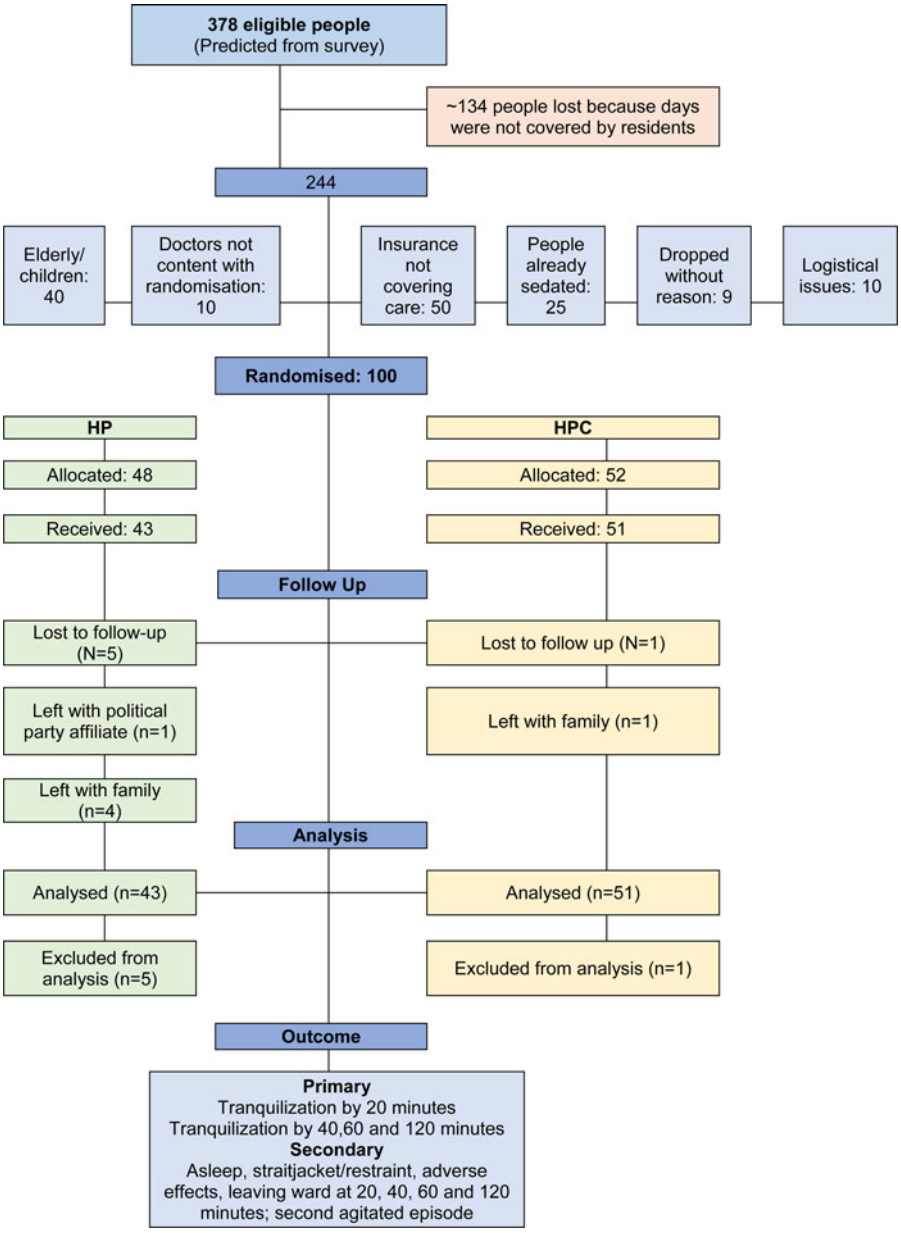

Fig. 1. Flow diagram.

successful randomisation. Patients were, on average, in their mid-30s, around half were experiencing their first psychiatric attendance and, unusually for a trial of this type, half were women. Also, in the opinion of these experienced staff, this group of patents were severely disturbed and thought to have a psychosis-related disorder. Most participants were already prescribed antipsychotic treatment before presenting to the hospital.

All patients who received the intervention were given 5 mg haloperidol, 25 mg promethazine and 100 mg chlorpromazine if they received the triple combination, and 5 mg haloperidol and 25 mg promethazine if they received the double combination. The attending doctors chose no variations of dose.

Of the 100 participants randomised, two families decided that they did not want their relative to be part of the trial and there was no more involvement and their data were withdrawn. Four people, again, post-randomisation, withdrew consent for participation and all their data were also withdrawn. Table 2 shows basic information collected at the point of randomisation with the presumed causes for the disturbance recorded blind to the group of allocation (before the envelope was opened) while Table 3 shows the main results.

According to the TREC-Entry form (See TREC-Protocol in supplementary material), the experienced staff thought and noted this group to be really quite disturbed and that the disturbance was most frequently due to a psychotic illness (schizophrenia or mania) despite the majority already being on antipsychotic drugs. Substance misuse as a primary cause of disturbance seems uncommon. Approximately half of the participants were women and half of the 100 were experiencing their first psychiatric attendance – although most of both groups were already on antipsychotic drugs – indicating that some treatment by community physicians is common before presenting at the hospital.

Baseline characteristics are evenly distributed between the two groups of allocation.

There were no clear differences between the two intervention groups when assessing RT. Around one-third of both groups were tranquil or calm by 20 min (30% CI 21–40).

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Table 2. Characteristics of patients at trial entry

		HP	HPC
Randomised	**Total**	**48**	**52**
	Withdrawn	5	1
	Completed	43	51
Characteristics			
Age			
	Mean	36 (s.d.: 12.3)	37 (s.d. 11.4)
	Median	35	36
Sex		***N* (%, 95% Cis)**	
Male	Total 45	21 (44%, 30–59)	24 (46%, 32–60)
Female	Total 49	22 (46%, 32–61)	27 (52%, 37–66)
Missing		5 (10%, 4–22)	1 (2%, 0–10)
First psychiatric attendance			
Yes		23 (48%, 34–63)	33 (63%, 50–75)
No		20 (42%, 28–57)	18 (35%, 22–49)
Missing		5 (10%, 4–22)	1 (2%, 0–10)
Severity of disturbance – first impression			
Moderately		4 (8%, 3–19)	1 (1%, 0–10)
Markedly		16 (33%, 21–48)	18 (37%, 24–51)
Severely		20 (42%, 29–56)	32 (61%, 48–74)
Among the most extreme disturbed		3 (6%, 2–16)	0 (0%, 0–8)
Missing		5 (10%, 4–22)	1 (1%, 0–10)
Presumed cause for agitation			
Psychosis (schizophrenia or mania)		27 (56%, 42–70)	30 (58%, 44–70)
Substance abuse		5 (10%,4–22)	3 (6%, 2–16)
Intellectual disability		1 (2%, 0–10)	3 (6%, 2–16)
Organic		0	0
Psychological		0	1 (2%, 0.1–12)
Unknown		10 (21%, 11–34)	14 (26%, 17–40)
Withdrawn		5 (11%, 4–22)	1 (2%, 0.1–12)
Already on antipsychotic medication			
Yes		41 (85%, 72–92)	44 (85%, 71–93)
No		2 (5%, 1–13)	7 (13%, 6–26)
Withdrawn		5 (10%, 4–22)	1 (2%, 0–10)

By 40 min, however, there did seem to be a clear – and important (18%) – difference between groups for this outcome. Around 25% (CI 17–34) of those allocated to HP were tranquil compared with 43% (CI 33–53) given the triple therapy (RR 0.66 CI 0.49–0.90). By 60 min – and 120 min – the difference was gone and around 80% of both groups were tranquil or calm.

As for the more extreme – but also the more concrete – outcome of 'asleep', events were less common in both groups, but, again, with no clear difference at 20 min. By 40 min around 20% (CI 13–28) of both groups were asleep. At the 1-h mark, statistically, significantly more people in the HPC group had fallen asleep but by 2 h this difference had disappeared. By this time around half of both groups were sleeping – 45% (CI 32–52).

The use of restraints and or straightjackets is well documented in Lebanese practice. It is part of routine care. At no stage was there an impression that one or other medication regimen influenced the use of this form of restriction. Initially (at 20 min) around 30% (CI 21–40) in both groups were restrained in this way. By 2 h this had decreased to approximately 9% (CI 4–16) in each group.

Adverse events were not recorded as residents did not perceive extrapyramidal symptoms (EPS) as a 'serious' adverse event. However, trihexyphenidyl is used in the treatment of EPS (a proxy measure of EPS) and just less than one-fifth of patients in both groups were treated for EPS post-randomisation.

Discussion

The trial sought to investigate whether the routine care of Lebanese psychiatric practice of adding chlorpromazine to the well-researched HP would have a meaningful effect on managing patients with an aggressive episode presenting to the psychiatric unit. This is not the first trial of its type but it is the first of this particular comparison and the first RT randomised trial in the Middle East. Lebanon is now one of the relatively few countries that have evaluated treatments used locally in this most difficult of clinical situations.

As with other trials, participants were highly disturbed people, most commonly thought to be psychotic and, although half were in their first episode, most were already on antipsychotic medication. Where they differed to other RT trials is that few were thought to have their aggression generated by misuse of substances and more were women. The former might be explained by the cultural context of the trial but the latter is not. Our survey predicted a 70:30 split for men and women but the trial is almost 50:50. We found no evidence of a selection bias at trial entry (Dib, 2020). We initially assumed that clinicians could have had a lower threshold of what constitutes an aggressive episode for women. This remains possible but the first impression of every individual presenting with an aggressive episode was recorded and results show both males and females were perceived as equally disturbed (86% markedly/severely disturbed; Table 2). It is also possible that this ratio may just have resulted from the play of chance.

TREC-Lebanon found no clear sustained benefit – or suggestion of benefit – of the added chlorpromazine in terms of becoming calm/tranquil, falling sleep, prevention of a further aggressive episode, or use of restraints – up to 12 h post-intervention – at least for those people for whom the clinician was unsure if the double or triple therapy would be best.

Measuring primary outcome at 20 min was a choice taken at protocol design. However, the short period until the primary outcome was recorded was clinically-driven as it was felt by front-line staff, in the emergency situation, if the aggression or agitation is not ended by that time the management of the situation is a failure and everyone is exposed to prolonged danger. The choice of time periods for the recording of the outcome, was not, however, chosen blind to past TREC trials.

'Calm/tranquil' was chosen by clinicians in Lebanon over 'asleep' as a primary outcome as they felt a situation in which clinician–patient interaction could resume was more desirable than sedation. However, patients who were asleep were mutually noted as calm and tranquil and, as per hospital policy, sleeping patients were no longer restrained.

https://doi.org/10.1017/S0033291720004869 Published online by Cambridge University Press

Table 3. Main results

	HP ($n = 48$)		HPC ($n = 52$)		Relative risk (CI)
	Event	Total	Event	Total	
20 min					
Calm or tranquil	14	48	18	52	0.84 (0.47–1.50)
Asleep	2	48	0	52	5.41 (0.27–109.87)
Straitjacket/Restraint	16	48	17	52	1.02 (0.58–1.78)
Unknown	0				
40 min					
Calm or tranquil	25	48	41	52	0.66 (0.49–0.90)
Asleep	9	48	9	52	1.08 (0.47–2.50)
Straitjacket/Restraint	13	48	10	52	1.41(0.68–2.91)
Unknown	0				
60 min					
Calm or tranquil	35	48	45	52	0.84 (0.69–1.03)
Asleep	10	48	25	52	0.81(0.23–0.81)
Straitjacket/Restraint	9	48	8	52	1.22 (0.51–2.90)
Unknown	0				
120 min					
Calm or tranquil	35	48	47	52	0.81 (0.66–0.98)
Asleep	18	48	24	52	0.81 (0.51–1.30)
Straitjacket/Restraint	5	48	6	52	0.90 (0.29–2.77)
Unknown	0				
Additional aggressive episode					
Recurrence	0	48	0	52	1.08 (0.02–53.47)
New episode	11	48	12	52	0.99 (0.47–2.80)
Serious adverse event	0	48	0	52	1.08 (0.02–53.47)
Adverse event (proxy)	7	48	11	52	0.73 (0.30–1.75)
By 2 weeks					
Discharged	34	48	39	52	0.97 (0.68–1.37)
Still hospitalised	9	48	12	52	0.84 (0.38–1.85)
Unknown	6				

If clinicians are faced with this difficult clinical scenario and the double or triple therapy is an option, and they are unsure which would be best in this particular situation, then not using the chlorpromazine option would seem prudent. Two drugs would seem better than using three – especially when using the double therapy of HP did not necessitate the need for higher doses in the absence of chlorpromazine. Simplifying the treatment down to one drug (haloperidol alone) has been compared with the double therapy in a randomised trial (Huf et al., 2007). Although the simple approach of giving just one drug rather than two would seem attractive and haloperidol alone is very widely used (Binder & McNiel, 1999; Pilowsky et al., 1992), this large clear trial was halted early as too many allocated to the single therapy (haloperidol) suffered acute dystonic reactions. The addition of promethazine added some sedation as well as a protective effect against the acute dystonia caused by use of haloperidol. TREC-Lebanon suggests that addition of chlorpromazine adds little to the potent, safe and well-researched combination of HP.

The staff did not observe any adverse events or effects that they considered 'serious'. Our design fault may have been to label this form '*serious* adverse events'. EPS were simply not recorded – and, on enquiry after study close, EPS were not designated as 'serious'. While it is well known that haloperidol does cause EPS and promethazine offsets these(Vella-Brincat & Macleod, 2004), it is highly unlikely that there were no EPS in a 100-person sample. Trihexyphenidyl is an antimuscarinic and is used in Lebanon in the treatment of the movement disorders commonly seen in EPS (Jilani, Sabir & Sharma, 2020) and use of any drugs are well recorded in patients' notes. We used this as a proxy adverse effect outcome. Trihexyphenidyl was used 18 times with no clear differences between groups (RR 0.73 95% CI 0.30–1.75).

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Limitations

TREC-Lebanon was undertaken in a large mental hospital of a complex low to middle-income country set in a region without a strong tradition of evaluation of psychiatric care through the use of trials. It ran on shoe-string funding because of the goodwill and energy of the staff – and partially because they had a hand in its design and it recorded outcomes of direct clinical interest. The use of fine-grain measures of aggression such as the overt aggression scale (OAS) (Yudofsky, Silver, Jackson, Endicott, & Williams, 1986) may have been able to highlight differences between the two treatment regimens when the simple binary outcome could not – at least with 100 participants. The survey had predicted the potential for more recruitment.

Past TREC trials – all similarly pioneering in that no identical comparison had been done before to provide benchmark evidence – were planned to illustrate a 15% difference between groups. This was a pragmatic choice based on the possibility for recruitment, an estimate of the difference needed to truly promote clinical change and educated guesswork gleaned from past TREC studies. There was always the danger TREC-Lebanon would be underpowered to highlight a true difference. However, with 25% incidence of outcome in the control HP group and a not inconceivable difference of 25% with the HPC group a total recruitment of 116 would have been adequate. However, now, with the final result of RR 0.84 and the accompanying 95% Cis of 0.47–1.50, there is evidence that, although a real difference could exist between the two regimens (around 5% at 30% incidence in control), for a trial to illustrate this with confidence, the recruitment would have to be around 1800 people. Now we know the study was underpowered to confidently illustrate a clear difference – but, we argue from the evidence of this trial, any existing difference at 20 min is too subtle to really matter. TREC-Lebanon was, however, not underpowered in the sense of illustrating to readers and the clinicians of Beirut and beyond that such studies can and should be done to refine thinking in this neglected area as well as clinical practice everywhere.

In addition, the more subtle outcomes that may have been possible to record using the OAS were not what the staff wanted. Simple and clear outcomes are what are used in everyday clinical life and it was these that were sought by the staff. For these outcomes, there are no suggestion of a sustained difference between the two drug regimens.

We had hoped to emulate the design in TREC-Rio (TREC Collaborative Group, 2003) where a person, independent of the care of the participant, accurately timed the period until the person was calm and then cross-checked this with the time recorded by the nurses. This proved impossible in the very limited resources available to us in Beirut. TREC-Rio (TREC Collaborative Group, 2003) showed that unblinded use of the simple timer and form resulted in accurate records. We have no reason to believe this is any different for TREC-Lebanon.

We would add an adverse effect checklist in a future design. The staff are sensitive to the many difficulties that people can encounter with the use of these drugs but the recording of the adverse effects is not comprehensive and, we think, a checklist would help.

Conclusions

TREC-Lebanon compared, for the first time, a triple RT therapy (HPC) against the much more widely used and tested HP combination. Few convincing clear differences were apparent. Where clinicians felt there was no contraindication to giving the drugs, when there was uncertainty over which was better to use, then the less complex, well-tested HP was swiftly calming.

TREC-Lebanon is an example of a randomised trial conducted because staff wanted to know the answer to a difficult – and unanswered – clinical question. There remain many unanswered questions as regards to RT techniques and we know there are many interested staff capable of generating a randomised trial design suitable to inform local and then wider practice. This neglected area of research should be properly funded and many more studies are strongly recommended to be undertaken across varied traditions of care.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720004869.

Author contributions. JD was involved in the study concept and design, acquisition, analysis, interpretation of data and drafting the manuscript. CEA and SH were involved in study concept and design. The TREC-Lebanon Collaborative Group were involved with trial design including administering and recording data. SH was the guarantor.

Members of the TREC-Lebanon Collaborative Group:
Data Monitoring Committee: GA and JM
Trial Steering Committee: PS and RH

We thank the administrative, medical, nursing and pharmacy staff of the Psychiatric Hospital of the Cross for their kindness, patience, interest and enthusiasm.

Financial support. The authors would like to thank the staff and sisters at the Psychiatric Hospital of the Cross.

Conflict of interest. None.

Ethical approval. The ethics division of the Institute of Mental Health, School of Medicine, University of Nottingham permitted JD to conduct the trial as part of his PhD thesis provided all data to be analysed were anonymised. The ethics committee of the Psychiatric Hospital of the Cross granted ethical approval. Ethics number: HPC-001-2018

Note

1 TREC, Tranquilização Rápida Ensaio Clínico [Rapid Tranquilisation – Clinical Trial] and follows in the tradition of the pragmatic trials designed, first in Brazil and then India.

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https://doi.org/10.1017/S0033291720004869 Published online by Cambridge University Press

Appendix

Table A1. Interventions used in Lebanese emergency practice

Intervention	Order of choice →	1st	2nd	3rd	4th	5th	6th
Non-drug	Verbal Command	1					
	Straitjacket	6	2			1	
Drug (all IM)	Diazepam	8	5	2	1		
	Haloperidol + Promethazine + Chlorpromazine	7	5	4	1	1	
	Haloperidol + Promethazine ± Benzhexol	4	4				
	Chlorpromazine + Lorazepam	2					
	Lorazepam	2	2	1			
	Zuclopenthixol + Promethazine	2				1	
	Chlorpromazine	1	3	3	2	1	
	Chlorpromazine + Promethazine	1					
	Diazepam + Lorazepam + Promethazine	1					
	Haloperidol	1					
	Haloperidol + Promethazine + Chlorpromazine + Lorazepam	1					
	Olanzapine	1					
	Zuclopenthixol	1				1	
	Promethazine		4	1	4	2	1
	Clozapine		1				
	Benzhexol			3			
Total		**39**	**25**	**14**	**8**	**7**	**1**

https://doi.org/10.1017/S0033291720004869 Published online by Cambridge University Press