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In: Manual therapy Supplement: “Terrestrial neuro-musculoskeletal rehabilitation for astronaut reconditioning: reciprocal knowledge transfer”

Guest Editors: Maria Stokes, Simon Evetts, Julie Hides

Methodology for astronaut reconditioning research

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ABSTRACT

Space medicine offers some unique challenges, especially in terms of research methodology. A specific challenge for astronaut reconditioning involves identification of what aspects of terrestrial research methodology hold and which require modification. This paper outlines this thesis and presents appropriate solutions where possible.

It is concluded that spaceflight rehabilitation research should remain question/problem driven and is broadly similar to the terrestrial equivalent on small populations, such as rare diseases and various sports. Astronauts and Medical Operations personnel should be involved at all levels to ensure feasibility of research protocols. There is room for creative and hybrid methodology but careful systematic observation is likely to be more achievable and fruitful than complex trial based comparisons. Multi-space agency collaboration will be critical to pool data from small groups of astronauts with the accepted use of standardised outcome measures across all agencies. Systematic reviews will be an essential component.

Most limitations relate to the inherent small sample size available for human spaceflight research. Early adoption of a co-operative model for spaceflight rehabilitation research is therefore advised.

Highlights

- Space research methodology parallels that for small terrestrial populations
- Small sample sizes in human spaceflight research pose challenges for study design
- Systematic evaluation of individuals may be the most achievable and fruitful approach
- Standardised outcome measures are needed across studies
- Multi-agency collaboration is vital to enable pooling of data

Key words: Observational, Study Design, IDEAL, rehabilitation, astronaut reconditioning

1. Introduction

Research methodology for space medicine can draw from established designs and practices, yet there are unique aspects to space which demand special consideration. The challenge is to identify which aspects of terrestrial methodology remain robust for space medicine, identify which aspects are inappropriate and then present solutions.

2. Study Design Challenges in Existing Literature / Knowledge

The methodological considerations unique to space medicine, including reconditioning are described in brief. Whilst evidence on treatment efficacy is preferably generated from randomised controlled trials (RCTs) and meta-analyses of such studies, the space medicine environment, with its extremely small population, restricts the use of such a design. Randomised N of 1 trials may have a limited role although they cannot address final rehabilitative outcomes (Lillie et al. 2011). Alternative and hybrid methods or modifications are required to generate the body of knowledge (see Fig 1), including;

- i. Assimilation, extraction and summation from existing studies (specifically on space reconditioning).
- ii. Translation from existing observational studies from the realms of physiology and psychology.
- iii. Evidence from directly related terrestrial studies of similar problems in relation to deconditioning.
- iv. Indirect evidence from corollary studies of hostile environments (these may have similar limitations to space travel research).
- v. New tailored and specifically designed interventional studies (accepting the small study size and restrictions inherent in the environment).

Designing new studies will be the most challenging and the majority of the present paper is given over to this.

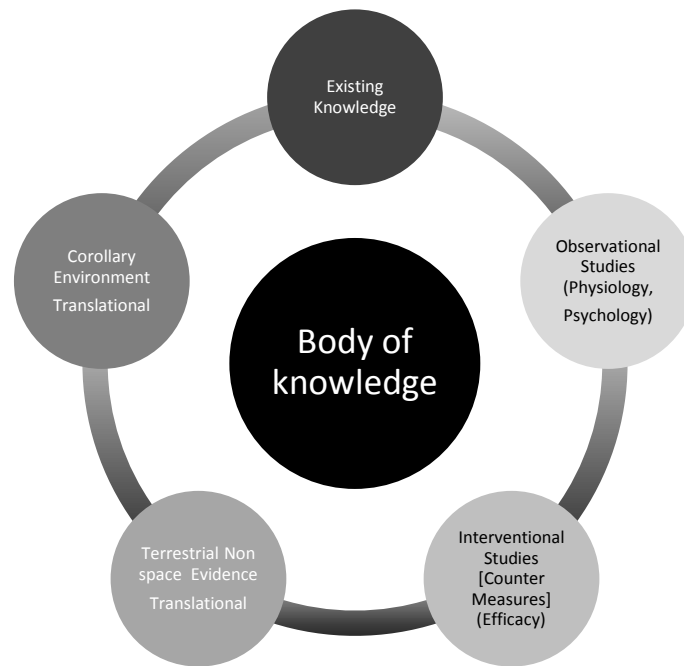


Figure 1: Schema of information source for reconditioning science and efficacy

2.1 First in human characteristics of interventions

One of the primary issues for evaluating interventions in space medicine, including reconditioning, is the small population of astronauts which could be included in a study. Here, similar characteristics are shared with other “first in [hu]man studies”, particularly with the surgical specialities. These studies are the first time the device or drugs have been used in/for human subjects and usually involve a very small number of participants. The very low ceiling on available participants (of astronauts) with the associated reduction in statistical precision to detect differences is of particular note and suggests that formal statistical analyses are not likely to be appropriate, except in very restricted and modified (accepted a much lower level of certainty than is commonly used) sense.

Realistically, the majority of space studies will have low numbers of participants and may span several years and multiple missions (Genc et al. 2010). As noted above this poses a challenge to robust statistical analysis. Statistical precision to show meaningful effects will be negligible without very strong assumptions based upon prior belief and/or data external to the current study.

2.2 Control of bias

A major issue will be control of bias. The previous lack of authoritative data and studies may have unintentionally introduced preference behaviour for specific interventions for space travel. For example, the inflight countermeasures exercise programmes differ between agencies, which may introduce bias to the results. Minimising this bias, including assessor bias, will be critical and interpretation will need to be cautious.

2.3 Account of unique and variable population

The study population is undoubtedly unique. This has implications for generalisability to other populations of new work outside any particular study, but perhaps more importantly, for related or external studies being used to support a specific hypothesis. Each astronaut is unique, and it is suspected, quite distinct from an “average” individual (reflecting high physical performance levels and psychological robustness). This introduces a challenge and consideration is needed to assess whether the variation between individual astronauts (intra-group) is considered with regard to more typical extreme individuals (normal population).

Advantages of the small astronaut population with a culture of furthering scientific understanding include: feasibility of recruiting the entire “captive” population, complete data return and good data sets, even in the early post-mission phase where they are closely monitored. Human space research also offers the unique opportunity to study deconditioning without the complications of pathologies, offering potential solutions for terrestrial rehabilitation.

2.4 Account of unique reconditioning goals

The content of reconditioning for space travel is a challenge to any study assessing efficacy of rehabilitation. The problems encountered and the goals of the intervention will be distinctive, so this limit of direct experience could be problematic. The small sample sizes and limited knowledge of normal variation in astronauts make it difficult to recognise outliers

in the data. An open mind will be required, yet organised “sense checking” by the research team will be paramount.

2.5 Timing of measurements and diffusion

Space travel research may not afford the flexibility of follow up assessment timing found in comparable terrestrial studies. The reasons for this include space mission related safety and operational duties, and the limited postflight contact with the astronaut beyond the period of supervised postflight reconditioning.

In addition, astronauts may be involved in many simultaneous medical experiments. There is unlikely to be contamination between effects of interventions because attempts are made to prevent astronauts being involved in multiple interventions. However, there is potential for effects from multiple measurements contaminating the results.

3. Optimum Study Designs for Future Space Life Science Studies

Accounting for Known Limitations in Existing Literature / Knowledge

There is no perfect study design solution for space related medical research and authoritative efficacy studies will be difficult to achieve. The optimal approach involves any design or method that reduces bias and provides the greatest level of external validity.

3.1 Systematic review and summary methods

The limited number of studies in space reconditioning lends itself to an amalgamation model to generate evidence. A systematic review approach should be considered with a broad inclusion of study designs. This has been demonstrated well in the recent literature review of Winnard et al (2016 current Special Issue). Systematic review and amalgamated data may result in loss of detail for some experiments, but this disadvantage is outweighed by achieving greater experimental numbers.

3.1 Addressing the problems of first in human characteristics of interventions

It is recommended that an ordered and systematic approach to prospective data collection is pursued, similar to that of IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up) recommendations for surgical sciences (McCulloch et al. 2009; McCulloch et al. 2013). The IDEAL is a systematic approach to the introduction of surgical innovation which consists of the five phases and the first two (idea and development), in particular, may lend themselves to postflight reconditioning. The first part of the IDEAL approach does not involve inferential statistics.

In terms of low sample numbers, rather than pretending that sufficient precision can be achieved, authority of subsequent studies will depend on the transparency and quality of data capture, choice of measurement variables/instruments and the ability to amass/assimilate compatible data, perhaps from wide ranging sources. A coordinated approach to data capture systems will help. Data analysis will therefore be informal and with each participant assessed on their own.

3.2 N of 1 Studies

The rarity of events and very small sample size in space medicine promotes designs such as an n-of-1 trial as a way to increase knowledge (Lillie et al. 2011). It is worth noting that the term “Single case study” is used inconsistently in the rehabilitation literature to describe a variety of study designs with a small number of participants ranging from a more extensive case-report of a single participant (e.g. Sakamoto et al. 1999; Sethy et al 2010) to a small prospective single group cohort design (Guzmán et al. 2016). Some of the studies which this term is applied to, share several of the positive design features of an n-of-1 trial.

The IDEAL group’s work on early surgical innovation (McCulloch et al. 2013) provides a basis for considering a more extensive approach to maximise the reporting of small, purely observational multiple individual studies regarding what occurred over time, when and why, as do some “Single case studies” (e.g. Flinn et al 2009; Lafond et al. 2008) . In this context of space rehabilitation science, an n-of-1 trial study design offers an attractive way to

maximise the return from a single participant's involvement as an experiment, if some degree of control can be exerted on the factors of interest and the study can be planned in advance. In this design, the participant acts as their own control in an intentional way so as to maximise the value of the data collected and the potential for meaningful inference. This can involve randomisation of the sequence of assessment periods and repetition of the exposure (e.g. treatment) of interest.

Although N of 1 studies are low on the conventional levels of evidence (e.g. in contrast to RCT's), they can still be used to describe outcome and establish certain facts, though not the likelihood of events occurring. N of 1 studies have the advantage of being sensitive to individual organism differences, are flexible and easily managed (Lillie et al. 2011). Additionally, standard design features such as randomisation and washout period can be used to minimise the risk of bias. They can, however, suffer from carry over effects and issues with ordering/sequencing the intervention. They are best used when multiple episodes of the same intervention can be applied (i.e. ABCABC design, for three interventions each trialled at two separate times). As an example, it might involve an intervention period inflight [A], then a wash out period postflight [B], then a different intervention period flight [C] etc.).

3.3 Case control studies

Case control studies might be considered a more robust method of forming evidence than N of 1 studies in that they can provide more generalisable findings. The higher sample size may also provide greater precision. However, the retrospective nature of case control studies, i.e. looking at the difference between individuals who have and who have not already experienced the event of interest is a distinct disadvantage. Additionally they are susceptible to unintended differences between cases and controls which may confound the finding. The sampling of cases and controls requires careful consideration with matching often used to limit the potential for such factors to influence the result though with uncertain success. Similarly to N of 1 studies, case control studies in astronauts could be

compromised by the multiple investigation model on a single mission i.e. the rarity of space travel means that astronauts are often encumbered with being participants for several simultaneous experiments. A limitation of this design for space research is the limited participant numbers available which makes investigation of rare events and the choice of controls particularly problematic.

3.4 Other approaches to optimise

In view of the above limitations the following strategies are recommended. The empowerment of purely descriptive studies through clear and systematic planning and reporting, use of internal controls (Cavanagh et al. 2009) where possible (including the single case design outlined above), observation of patterns (to gauge safety), the use of modelling techniques (such as those used in joint force understanding and implant manufacture (Feikes et al. 2003; Kumar et al. 2012), and appropriate adaptive designs where immediate outcomes can be used to inform design modifications (Wassmer 2004). A pressing requirement might be to standardise data collection protocols across space agencies to enable pooling and sharing of data. This will substantially increase the usefulness of individual studies. All efforts should be made to achieve optimised follow up and essential data sets incorporating key outcome measures should be established. The COMET initiative (<http://www.comet-initiative.org/>) would be useful resource for conducting this process.

3.5 Mixed methodology and qualitative work

Consideration should be given to mixed methods research (which combines quantitative and qualitative methods) and particularly qualitative studies to delineate or focus any specific research questions. Interviews with astronauts will be especially important to direct future investigations.

3.6 Transferable designs – translation capability

A sensible approach is to take advantage of terrestrial rehabilitation research, particularly where similar problems exist such as in rare diseases, elite sports, neurological conditions. When designing studies it is recommended that (providing sufficient quality exists) the terrestrial equivalent of the study is used as an initial basis. The use of standardised outcome measures and universally agreed time-points for measurement would help in this goal.

3.7 Involvement of astronauts and medical operations experts

Patient and public involvement (PPI) in research is becoming routine in terrestrial research. A space medicine equivalent is appropriate and required. Astronauts have direct knowledge and insight into the unique issues experienced during and after spaceflight. Medical Operations experts are also key to informing research at all stages. Focus groups, and directed feedback processes should be considered to achieve these goals, involving both astronauts and Medical Operations. There are various terrestrial bodies which have harnessed this need. The James Lind Alliance is an organisation that is dedicated to involving users in research and their model may be useful to follow (<http://www.jla.nihr.ac.uk/>). INVOLVE (www.invo.org.uk) is an organisation dedicated to meeting patients' needs in research. Although large scale PPI in the space fraternity may not be possible, there is need for some provision to be put in place.

4. OUTCOME MEASURES

4.1 Overview

Existing, well established and validated outcome measurement tools should be used, whenever possible. Where space specific tools have been developed these should be assessed comprehensively for face, construct, content and criterion validity before being used (Mokkink et al. 2010; Scholtes et al. 2011). Content validity is important in that it

demonstrates that any measure is comprehensive and covers all aspects under investigation. Reliability should also be established in the spaceflight environment and not assumed to be similar to terrestrial data (Mokkink, Terwee 2010; Scholtes, Terwee 2011).

The outcome measures used should also fit with the World Health Organisation (WHO) international classification of diseases and measurement. The relatively more recent International Classification of Functioning, Disability and Health (ICF), is a classification of the health components of functioning and disability (Ustun et al. 2003). The system allows evaluation of various domains including impairment, disability and participation. For example a torn back ligament (impairment) may produce an inability to extend an astronaut's back (disability), and also a restriction in being able to move about the spacecraft or spacewalk (participation limitation).

Examples of outcome measures that should be considered for space related reconditioning studies include: general health questionnaires (Chen et al. 2015); movement screening tools for assessing quality and control of movement, and functional tasks (Hides et al 2016); gait analysis variables (including moments and forces)(Genc, Gopalakrishnan 2010); and EMG profiling (Layne et al. 1997).

4.2 Physical/clinical assessment tools

These should not necessarily differ from terrestrial instruments, providing they can be applied in space and by appropriate personnel (if assessment is required in space). Teaching of testing protocols may be required for astronauts. These tests may include, e.g. specific range of movement, strength, function tests, directed at a (WHO) impairment level (Ustun, Chatterji 2003), such as joint stiffness, muscle weakness or inability to perform a particular task.

4.3 Outcomes specific to space travel reconditioning

Some tests have been developed specifically for space related evaluation, both during and post-mission. These include a variety of functional, balance and postural tests

(Bloomberg et al. 2003; Bloomberg et al. 2015; Bloomberg et al. 1997; Brady et al. 2009; Mulavara et al. 2010; Newman et al. 1997; Reschke et al. 1998). These evaluation techniques include the postural stability tests described by Bloomberg et al (Bloomberg, Peters 1997) and NASA's Functional Task Test (Arzeno et al. 2013). Technologies may be suitable for use in monitoring muscle status postflight to assess the effects of exercise programmes. For example, rehabilitative ultrasound imaging (RUSI) of muscle is used increasingly in terrestrial rehabilitation research (Whittaker et al. 2007) and is already being used by the ESA physiotherapist (Lambrecht et al 2016; in current Special Issue) to monitor recovery from muscle atrophy. A relatively new portable device (MyotonPRO) for non-invasive measurement of muscle mechanical properties (e.g. tone, stiffness and elasticity), has been tested in terrestrial cohorts (healthy and clinical) and found to be valid (Ditroilo et al. 2011), reliable (Chuang et al. 2012) and sensitive to the effects of ageing (Agyapong-Badu et al. 2016) and pathologies such as Parkinson's disease (Marusiak et al. 2012) and stroke (Chuang et al. 2012), as well as being sensitive to change after intervention (Marusiak et al. 2012). The device was found to be robust for testing astronauts on parabolic flights (Schneider et al. 2015). This technology therefore has the potential to measure the effect of spaceflight on the mechanical properties of muscle, which indicate muscle status in relation to strength and electrical activity that are not possible to monitor inflight (when preparing for surface missions on planets i.e. preconditioning) or routinely postflight.

4.4 Patient reported outcome measures (PROMs)

Patient reported outcomes have enjoyed much recent popularity in medical research (Ashford et al. 2015; Kearney et al. 2012; Lee et al. 2013; Worth et al. 2012). Such measurement instruments report the self-perceived status of how a person's condition is impacting on them. Several "off the shelf" instruments may be of value for assessing reconditioning effectiveness, including activity scores and self-report functional scores (Briggs et al. 2009; Kocher et al. 2004).

Whilst the use of existing tools is advised, some consideration should be given to the extended remit of these instruments. As in the case of NHS PROMs (UK) the use of patient reported outcome measures have sometimes outstretched their original design purpose without revalidation (Harris et al. 2013) PROMs are self-reported outcome measurement tools (questionnaires) that have usually been designed for a particular purpose and their measurement characteristics usually only hold when used for the intended purpose. Using outside the remit gives potential for incorrect or uninterpretable results.

If appropriate, there may be the opportunity to develop new PROMs for space related research, directed by astronaut and medical operations involvement. It will be particularly important to ensure the tools are valid for measuring response over time. Hence, the tools should also have good sensitivity to change (viz. both types of minimal clinically important difference; MCID), the calculated Minimal Important Change (MIC) / Minimal Important Difference (MID) values, and repeatability. The MIC or MID is the minimally important change or difference between groups in a variable that is deemed clinically important or relevant. These measures of clinically important change are distinct from the minimal detectable change (MDC) which relates only to how measurable changes are. Without these values it is difficult to ascertain what changes in health status are actually measurable or are important (Beard et al. 2015). Given the low number of astronauts, it might be that these measures of precision will need to be established in terrestrial studies that inform space R&D.

5. Conclusion

Most limitations to the methodology of evaluating human spaceflight effects relate to the inherent small sample size available. There are several unique aspects to space medicine research and these nearly all apply to the domain of reconditioning. Several of the limitations can be addressed but many of the issues, including the small sample size problem, will remain challenging.

6. Recommendations

- Involvement of astronauts and Medical Operations experts is essential for identifying relevant problems and ensuring feasibility of research protocols
- Assessment of each clinical issue/problem on an individual basis may be appropriate.
- Careful observation will be the mainstay.
- Use standardised outcome measures and universally agreed time-points for measurement
- Pull knowledge and information from relevant terrestrial population where appropriate. e.g. clinical disorders seen in terrestrial populations involving deconditioning.
- Multi-space agency collaboration to share research protocols and pool data from small groups of astronauts to enable important advances in human space research.

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