Effect of acute intermittent hypoxia to enhance motor functions in adults with incomplete spinal cord injury – A systematic review and meta-analysis

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Author contributions

BB and JP independently conducted the selection process and extracted data. GE and ES wrote the manuscript. ARD contributed to data interpretation and manuscript revisions. All authors read and approved the final manuscript.

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The data that support the findings of this study are available on request from the corresponding author, GE.

Abstract

Objective: This systematic review aimed to assess the safety and effectiveness of acute intermittent hypoxia to improve motor outcomes in individuals with incomplete spinal cord injury.

Data source: Pubmed, Embase, Scopus and Cochrane Library databases were searched.

Review methods: We only included randomised controlled trials (published up to September 2025) that met the following criteria: participants were adults with incomplete spinal cord injury; the intervention involved acute intermittent hypoxia with or without motor training; the control group received sham acute intermittent hypoxia with or without motor training; outcomes included motor functions. Risk of bias was evaluated using RoB2 tool. Risk and mean differences were computed, with a random-effects model.

Results: Nine randomized controlled trials (n=114) were included. Overall risk of bias was with some concerns. The review indicates that acute intermittent hypoxia is safe and has good treatment adherence, with low drop-out rates for acute intermittent hypoxia alone (RD=0.08; 95% CI: -0.11 – 0.26; I^2=0%; n=66) or with gait training (RD=0.04; 95% CI: -0.11 – 0.18; I^2=0%; n=57). Acute intermittent hypoxia was found to have beneficial effects on walking speed (MD=5.97; 95% CI: 1.4 – 10.54; I^2=0%; n=53), endurance (MD=39.39; 95% CI: 1.92 – 76.86; I^2=50%; n=54), muscle strength, and manual dexterity. However, no significant effects were observed on balance functions.

Conclusion: Acute intermittent hypoxia may be a promising adjunctive therapy to enhance motor function in individuals with incomplete spinal cord injury. Further research with standardised protocols and larger sample sizes is needed to optimise its use in clinical practice.

Keywords: Spinal cord injuries; Hypoxia; Rehabilitation; Gait; Meta-analysis

Clinical message

- Acute intermittent hypoxia is a therapeutic approach involving brief, repeated episodes of breathing air with reduced oxygen levels, interspersed with periods of normal oxygenation to allow recovery.
- Acute intermittent hypoxia appears to be a safe intervention, and there is low to very low certainty evidence suggesting that it may improve walking speed, endurance, muscle strength, and manual dexterity in individuals with incomplete spinal cord injury.
- Findings of this work do not support a significant effect of acute intermittent hypoxia on balance outcomes.

Introduction

Spinal cord injury is a significant public health concern, with an estimated global prevalence of 20.6 million individuals.[1] Individuals with spinal cord injury commonly experience sensorimotor impairments, including sensory deficits, pain, muscle weakness, or paralysis.[2] The condition is frequently associated with long-term disability, reduced quality of life, and diminished life expectancy.[3] Individuals with incomplete lesions typically show the greatest response to rehabilitation interventions, indicating that the effectiveness of such interventions is closely tied to the extent of spared spinal cord neurons.[4] While some degree of spontaneous plasticity may occur, leading to partial recovery of motor ability, these improvements are often insufficient for independent activity.[5]

Acute intermittent hypoxia has emerged as a promising intervention, activating rapid mechanisms of spinal synaptic plasticity and enhancing both respiratory and non-respiratory motor function in animal models of incomplete spinal cord injury.[6-8] Acute intermittent hypoxia is a therapeutic technique that involves brief, repetitive cycles of breathing air with reduced oxygen levels (hypoxia), alternated with periods of normal oxygen levels (normoxia) to allow recovery.[9] Recent studies have demonstrated that acute intermittent hypoxia improves breathing capacity as well as motor function in individuals with incomplete spinal cord injury.[10-12] Moreover, combining acute intermittent hypoxia with task-oriented interventions, such as treadmill training, has shown superior motor outcomes compared to task-specific interventions alone.[13, 14]

Despite growing interest in the use of acute intermittent hypoxia to enhance recovery in individuals with incomplete spinal cord injury, current systematic reviews on the topic are limited in scope and methodological rigor. Three reviews without pooled analysis have been published to date.[15-17] However, they present several important shortcomings. First, in all these reviews, results were summarized narratively or by reporting single-study effect sizes,

which limits interpretability. Pooling results from multiple studies through meta-analysis offers a more quantitative and objective approach, providing precise effect estimates, identifying patterns and heterogeneity across studies, resolving conflicting findings, and ultimately yielding more robust and transparent conclusions than narrative summaries. Second, none of the prior reviews assessed the certainty of evidence, despite its central role in PRISMA reporting and its importance for informing clinical decision-making. Third, none of the reviews evaluated treatment adherence. Yet, adherence to AIH protocols is a critical element for successful implementation in clinical practice and for understanding the feasibility of translating this intervention to real-world settings. Moreover, several of the studies included in those reviews did not isolate the effects of AIH but rather combined it with pharmacological agents, caffeine, or electrical stimulation, confounding the interpretation of results.

Given these limitations, there remains a need for a rigorous and comprehensive synthesis of the evidence. This systematic review is, to our knowledge, the first to provide a quantitative analysis of AIH in participants with SCI using meta-analyses of randomized controlled trials, while excluding studies with interfering interventions. We further apply standardized tools to assess methodological quality and to evaluate the certainty of evidence, and systematically examine adherence to AIH protocols. By addressing these critical gaps, our review not only provides a more reliable estimate of AIH efficacy but also delivers clinically actionable insights that may inform the development of future guidelines.

Methods

We conducted this work in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines[18], and prospectively published the review protocol to PROSPERO (CRD42024512313).

We included the trials if they comply with all the following criteria: (P) participants were adults with a confirmed diagnosis of incomplete spinal cord injury; (I) the experimental group received acute intermittent hypoxia intervention (any controlled pattern of oxygen deprivation that is applied intermittently and for short durations) paired or not with motor training (as defined by the authors), regardless of frequency and duration of cycles, with no restriction on treatment intensity, duration and number of sessions, and coupling between acute intermittent hypoxia and motor training (intervention provided before, during, or after acute intermittent hypoxia); (C) the control group received sham acute intermittent hypoxia paired or not with motor training; (O) relevant outcomes were measured to assess the ICF-WHO motor and cognitive functions or activity components; (s) the study followed a randomized controlled trial design, was written in English, French, or Spanish, and was published before September 2025.

Search methods, trials selection, data extraction and risk of bias assessment

We first elaborated a search strategy for PubMed database using the MeSH terms "hypoxia" and "spinal cord injuries" with their synonyms and variants. We then adapted this strategy for Embase, Scopus and Cochrane Library databases (Table 1). Databases were search from inception to September 2025 (n = 520 records identified).

After extracting the references from the databases, two independent authors stored them in a reference management software (EndNote). They excluded duplicates and conducted a first trial selection based on titles and abstracts. They followed the same

procedure to perform a second screen and selection based on the full texts. A third investigator hand-searched the reference lists of all included studies, relevant reviews identified during the searches, and conference papers. We then organised a meeting to discuss discrepancies and to find consensus about the trials to be included in the work.

Once the articles were selected, we collected the following data for each article: type and content of intervention (in the control and intervention groups), time since diagnosis of the disease, age, sex (proportion of men and women), number of participants, method of evaluation of the intervention effect, and main findings. All data were extracted from the texts, tables and figures by two independent authors.

Two independent authors assessed the risk of bias using the Cochrane Risk of Bias 2 (RoB2) tool and its adaptation for cross-over RCTs.[19] RoB2 enables to assess the risk of bias of each RCT outcome across five different domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. For cross-over RCT an additional domain was added: bias arising from period effect and carryover effect.

For this project, we used the Excel version of RoB2. After entering all the information in the form, we used the file's algorithm to estimate, for each study (and for each variable), the risk of bias for the different domains and an overall risk of bias. The risk of bias was classified as low, with some concerns or high.

For outcomes reported in more than 10 studies, funnel plots were used to detect small study effects, potentially indicating publication bias. If asymmetry or outliers were present, the Egger regression test was performed to assess the impact of publication bias. For

outcomes reported in fewer than 10 studies, trial registries were reviewed to identify potential unpublished studies.

Statistical analysis

We used RevMan software for all statistical analyses. As we expected a certain amount of statistical heterogeneity, we chose a random-effects model.

When two or more randomized controlled trials reported statistical data on effectiveness or adherence for the same variable, we conducted a meta-analysis. If a meta-analysis was not possible, we synthesized the results according to the Synthesis Without Meta-analysis guidelines.[20]

For dichotomous outcomes, we determined the risk difference by considering the events and sample size in each intervention and control group. For continuous outcomes, to assess the difference in effectiveness between acute intermittent hypoxia therapy and sham interventions, we calculated, for each variable, a mean difference between the mean changes (post-intervention scores – baseline) of the experimental groups and those of the control groups. We were able to use the mean difference instead of the standardised mean difference because the included studies systematically used the same scales. To calculate the mean difference, we used, for each group, the mean changes, standard deviation and the number of participants. When the data were median and quartiles, we used the method of Wan et al. to convert them into means and standard deviations.[21] Similarly, we converted the confidence intervals and standard errors of the means into means and standard deviations using the methods described in the Cochrane handbook.

We analysed between-study clinical heterogeneity by examining and comparing their population, interventions (experimental and control) and outcomes. The studies had to be sufficiently similar to be statistically combined. We assessed statistical heterogeneity using

the I^2 index, which we interpreted as low for values < 30%, moderate for values 30% ≤ x < 50%, substantial for values 60% ≤ x < 80% and considerable for values ≥ 80%.

Lastly, we used the GRADE approach to assess the certainty of the evidence for each outcome.[22] This method enables to deliver a level of evidence (categorised as high, moderate, low, or very low) for each outcome according to study limitations, inconsistency, indirectness, imprecision, and publication bias. For each of these domains, the certainty of evidence must be lowered by one level for serious concerns and by two levels for very serious concerns.

Results

The search yielded a total of 520 records. After the removal of duplicates (n = 243), we screened 277 trials based on their titles and abstracts. This resulted in the inclusion of 34 articles for full-text triage. Main reasons for exclusion at full text review included irrelevant population (n = 1), irrelevant intervention (n = 4), irrelevant outcome (n = 8), not a randomized controlled trial (n = 6) and conference abstract (n = 5). Among these, 9 studies[11-14, 23-27] were retained for the qualitative and the quantitative synthesis. In Figure 1, we present a flow chart diagram illustrating the selection process.

As presented in Table 2, participants' mean age was of 45(2.6) years old. Total sample size of the included studies ranged from 6 to 35 participants. Female were present in all studies except one [12]. Participants' American Spinal Injury Association Impairment Scale score ranged from C to D. On average, at the moment of the study, participants' mean time since incomplete spinal cord injury diagnosis was of 8.3(5.76) years. All included studies received financial supports. Most randomized controlled trials[11, 12, 23, 25-27] (n=6) were conducted in the USA. The remaining three publications[13, 14, 24] present findings on various outcomes from a single study conducted in Chile.

Regarding the content of the interventions, acute intermittent hypoxia was provided alone in three studies[23, 25, 27], combined with a gait training in three different studies[11, 13, 14, 24, 26] and combined with hand opening practice in one study.[12] The total duration of the intervention programs ranged from one single session of 30 minutes to five consecutive days of 90 minutes sessions. Regarding the control groups, in all studies the content of the programs matched this of the intervention group except that acute intermittent hypoxia was replaced by sham acute intermittent hypoxia. Similarly, total duration of the programs in the control group also matched this of the intervention group.

As presented in Table 3, three studies[11, 13, 26] focused on walking speed and endurance, two[12, 25] on manual dexterity and hand use, one[23] on upper limb muscle strength and activity, one[27] on lower limb muscle strength and activity, one[14] on balance, and one safety (effect on memory deterioration).[24]

Overall risk of bias was considered as with some concerns in all randomized controlled trials[11-14, 23-27]. Detailed risk of bias per domain and for each outcome is presented in Supplementary File 1.

Safety and treatment adherence

No serious nor non-serious adverse events were reported in any of the included studies.

Oxyhaemoglobin saturation was measured in five studies.[11, 12, 14, 26, 27] During hypoxic episodes, depending on the studies, mean oxyhaemoglobin saturation of the intervention group varied between 78 and 85%, which remains safe according to the limit set by authors (>75%).[11] In the study of Hayes et al., higher values (mean=81.9(1.0) vs 78.0(1.5)) were observed for the group where acute intermittent hypoxia was combined with a gait training.[11]

Heart rate was measured in four studies[11, 12, 26, 27]. Hayes et al., reported mean changes of 5.7(0.4) ppm when participants followed acute intermittent hypoxia alone and 4.4(0.8) when combined with gait training.[11] Tan et al., reported a mean change of 2(0.8) ppm after five consecutive days of acute intermittent hypoxia combined with gait training.[26] In 2012, Trumbower et al., mentioned an increase in heart rate across all participants after the exposure to acute intermittent hypoxia but did not provide the effect size.[27] In 2017, when combined with hand opening practice, Trumbower et al., reported no difference in heart rate following 5 consecutive days of acute intermittent hypoxia.[12]

Blood pressure was measured in three studies[11, 12, 26]. Hayes et al., found no change in arterial blood pressure after exposure to acute intermittent hypoxia.[11] Tan et al., reported a small but significant decrease in systolic blood pressure (106.9(4.5)-100.1(2.0) mmHg) and a non-significant decrease in diastolic blood pressure (65.2(2.2)-63.4(1.5) mmHg) after the 5 days intervention.[26] Trumbower et al., did not find any significant difference on blood after the exposure to acute intermittent hypoxia.[12]

Hayes et al. reported that the exposure of acute intermittent hypoxia did not significantly affect spasticity nor overall cognition as measured by the Spinal Cord Assessment Tool for Spasticity and the Mini Mental State Examination, respectively.[11] Trumbower et al. also found no change in overall cognition following the acute intermittent hypoxia intervention.[12] Opazo et al. reported that the percentage of participants in the intervention group who observed an increase in spasticity (24%) and pain perception (11%) was not different that this of the control group (spasticity=31%; pain perception=25%).[13]

Episodic verbal and visual memory function were evaluated in one study using the Spanish Complutense verbal learning test and Rey-Osterrieth Complex Figure Test, respectively.[24] Navarrette-Opazo et al. assessed these functions to determine whether acute intermittent hypoxia combined with gait training might have deleterious effects on cognitive performance. They hey found that acute intermittent hypoxia did not affect episodic visual memory function and improved episodic verbal memory function (compared to baseline) across immediate, short-term, and long-term recall components. However, despite better verbal performance following the acute intermittent hypoxia intervention, the improvement was not statistically significantly different from the placebo group ($p>0.05$).[24]

Regarding treatment adherence, drop-outs were reported in two different studies[11, 13, 14, 24]. In the study of Hayes et al., two participants firstly allocated to the acute intermittent hypoxia group and one participant firstly allocated to the acute intermittent hypoxia combined

with gait training withdrew from the study. Reasons mentioned were travel costs, drug change and chronic pain, and schedule issues. In the study of Opazo et al., during each program (acute intermittent hypoxia combined with gait training vs sham acute intermittent hypoxia combined with gait training), one participant withdrew from the study. Reasons mentioned were moving to another city (intervention) and diagnosis of knee tendinitis (control).

As presented in Figure 2, concerning the probability of observing a drop-out, the risk difference between acute intermittent hypoxia and sham acute intermittent hypoxia appears non-significant (RD=0.08; 95%CI:-0.11–0.26; p=0.40; I^2=0%; 46 participants, 4 studies). Similarly, for interventions combining (sham) acute intermittent hypoxia with gait training (RD=0.04; 95%CI:-0.11–0.18; p=0.63; I^2=0%; 57 participants, 3 studies), and (sham) acute intermittent hypoxia with hand opening practice (RD=0.00; 95%CI:-0.46–0.46; p=1.00; 6 participants, 1 study) the risk difference between intervention and control groups seems non-significant.

Effect of acute intermittent hypoxia on walking speed, walking endurance, and balance

Three studies evaluated walking speed using the Ten Meter Walk Test[11, 13, 26]. As presented in Figure 3, when combined with gait training, acute intermittent hypoxia appears to lead to significant benefits in the Ten-Minute Walk Test over sham acute intermittent hypoxia combined with gait training (MD=5.97 s; 95%CI:1.40–10.54 s; p=0.01; I^2=0%; 53 participants, 3 studies). The observed effect size (MD=5.90 s) appears to be over the minimal clinically important difference mentioned in the scientific literature (0.5-1.3 s or 0.05-0.13 m/s).[28, 29] The significance difference between groups in favour of acute intermittent hypoxia was observed 2 weeks after the intervention in the study of Tan et al. (95%CI:0.6–10.5 s, p=0.03) [26] but was not observed at 3 days nor 7 days in the study of Hayes et al.[11]

Hayes et al. also evaluated the effectiveness of acute intermittent hypoxia when provided alone.[11] Authors reported that right after the intervention, benefits of acute intermittent hypoxia were higher but not significantly different than these of the control intervention. However, 7 days after the intervention, changes in the 10 Meter Walk Test were significantly higher after the acute intermittent hypoxia exposure than the sham intermittent one (95%CI:0.9–6.7 s, p=0.010).

Three studies evaluated walking endurance using the Six Minute Walk Test. As presented in Figure 4, when combined with gait training, acute intermittent hypoxia may lead to significant benefits in the Six Minute Walk Test over sham acute intermittent hypoxia combined with gait training (MD=39.48 m; 95%CI:2.32–76.63 m; p=0.04; I^2=50%; 54 participants, 3 studies). The observed effect size (MD=39.48 m) appears to be over the minimal clinically important difference mentioned in the scientific literature (36-39.6 m or 0.10-0.11 m/s).[30] The significance difference between groups in favour of acute intermittent hypoxia was observed 3 days after the intervention in the study of Hayes et al., (95%CI:46.4–269.2 m, p=0.001)[11] and one week post-intervention in the study of Tan et al.[26] However, for the latter, the difference became non-significant at two weeks follow-up.[26]

When provided alone, Hayes et al., reported that acute intermittent hypoxia led to improvements in walking endurance but not significantly superior to these of sham acute intermittent hypoxia. This non-significant between groups difference was also observed 3 days and 7 days following the intervention.[11]

One study evaluated the effect of acute intermittent hypoxia combined with gait training on standing and dynamic balance using inertial sensors.[14] For standing balance, authors measured the normalised jerk and root mean square of sway. For dynamic balance, authors measured turning duration, number of steps during a turn, and turn-to-sit duration during the Timed-Up and Go Test.

Results of this study showed that there was no significant difference between the effects of acute intermittent hypoxia combined with gait training and sham acute intermittent hypoxia combined with gait training on normalized jerk and root mean square of sway. Contrastingly, authors observed that the combination of acute intermittent hypoxia with gait training led to significantly greater reduction of the turning and turn-to-sit duration, and greater increase in the number of steps during a turn when compared to sham acute intermittent hypoxia combined with gait training.

Effect of acute intermittent hypoxia on muscle strength, muscle activity and manual dexterity

Afsharipour et al., evaluated elbow muscle strength and activity thanks to load cell and high density surface electromyography.[23] In their study, they showed that the increase in elbow flexion and extension strength following acute intermittent hypoxia exposure was significantly higher than following sham acute intermittent hypoxia. They also found that acute intermittent hypoxia led to significant increase in the root mean squared amplitude of the electromyography during maximal elbow flexion and extension but not sham acute intermittent hypoxia.

In their study, Sandhu et al., evaluated grip and pinch strength using Jamar and digital hand dynamometers.[25] Authors found that change in grip strength after a single session of acute intermittent hypoxia was significantly greater than after sham hypoxia at all time points for the left side (from 0 to 24 hours post-intervention) and almost all-time points (except right after the intervention). Regarding pinch strength, authors reported that significant larger changes after a single session of acute intermittent hypoxia over sham acute intermittent hypoxia were only found for the right hand at specific time points (from 30 min to 2 hours, 5 hours and 24 hours post-intervention).

In 2012, Trumbower et al., evaluated ankle muscle strength and activity using dynamometer and electromyography.[27] Authors reported that maximal voluntary torque increase in plantar flexion had values at 30 and 60 minutes post-intervention both significantly greater after acute intermittent hypoxia than in sham trials (p=0.02).

In 2017, Trumbower et al., evaluated hand aperture and muscle activity during maximal hand opening using optical motion analysis diodes and surface electromyography electrodes. Authors found that intermittent combined with hand-opening practice significantly improved maximum hand aperture by an average of 8.1(2.7) mm in 5 out of 6 participants, compared to both baseline (p=0.018) and sham practice (p=0.030). Additionally, 5 participants showed improved electromyography activity with daily acute intermittent hypoxia sessions (p=0.029), while sham practice had no significant effect on baseline electromyography activity (p=0.606).

Two studies evaluated manual dexterity using the Box and Block Test, the Nine Hole Peg Test and the Jepsen Taylor Hand Test.[12, 25]

Sandhu et al. reported that following a single session of acute intermittent hypoxia, the Box and Block Test scores showed significant improvement, increasing from 44.4(2.8) at baseline to 51.3(3.8) at 24 hours (p=0.001), exceeding the clinically relevant change threshold of 5.5 points.[25] In contrast, sham acute intermittent hypoxia showed no significant change in Box and Block Test scores at any time point. No significant changes were observed in the Nine Hole Peg Test scores after any intervention.

In the study of Trumbower et al. acute intermittent hypoxia combined with hand-opening practice led to improved Box and Block Test scores in all six participants compared to sham practice (p=0.016). Four participants also reduced their Jebsen-Taylor Hand Function test time after daily acute intermittent hypoxia practice compared to sham practice (p=0.078).

Certainty of the evidence

The certainty of evidence for the effects of acute intermittent hypoxia compared to sham acute intermittent hypoxia for rehabilitation in individuals with incomplete spinal cord injury is summarised in Table 4.

For treatment adherence, walking speed, muscle strength and activity, and manual dexterity, the certainty of evidence was rated as low due to a risk of bias with some concerns and imprecision related to small sample sizes. For walking endurance, the certainty of evidence was very low, downgraded for the same reasons, with the addition of inconsistency stemming from between-studies heterogeneity. Balance was also associated with very low certainty of evidence, primarily due to important imprecision (reliance on a single study) and a risk of bias with some concerns.

Discussion

The results of this work, including 9 randomized controlled trials, suggest that acute intermittent hypoxia is a safe intervention for individuals with incomplete spinal cord injury, although the certainty of evidence remains low to very low. Acute intermittent hypoxia demonstrated positive effects on several outcomes, particularly walking speed, endurance, muscle strength, and manual dexterity, supporting its role as an adjunct to conventional rehabilitation. However, the effect on balance was not significant.

None of the included studies reported any adverse event. High adherence was also reported with only few dropouts in two studies[11, 13, 14, 24] with reasons unrelated to the treatment. This aligns with previous works reporting that intermittent hypoxia is generally safe, particularly in the context of therapeutic applications.[9, 31] However, while mild exposure to acute intermittent hypoxia appears safe, severe exposure to it, such as in the protocol of Tamisier et al. (FiO2 of 13% for 14 consecutive days), may result in elevated blood pressure and increased sympathetic activities.[32]

The results of this review indicate that combining acute intermittent hypoxia with gait training yields greater improvements in walking speed, walking endurance compared to gait training alone. These findings suggest that acute intermittent hypoxia may enhance the effectiveness of task-specific rehabilitation approaches. Additionally, we found that, when applied as a standalone intervention, acute intermittent hypoxia can significantly improve both walking speed and endurance. Evidence suggests that acute intermittent hypoxia strengthens synaptic connections within the spinal cord, mediated in part by serotonin and new BDNF synthesis.[6, 9, 33, 34] In animal models, BDNF administration after spinal cord injury improved stepping performance[35, 36], and treadmill training enhanced both locomotor function and BDNF expression in spinal motoneurons.[37] Acute intermittent hypoxia may therefore serve as a potential adjunct to gait training to potentiate its effects on walking functions.

One included study, Naverrete-Opazo et al., investigated the effects of acute intermittent hypoxia combined with gait training on standing and dynamic balance.[14] Improvements were observed in dynamic balance but not in standing. This may be explained by the principle of task-specific training in individuals with spinal cord injury. Supporting this, De Leon et al.[38], showed in a spinal cord injury model that cats trained in either stepping or standing improved only in the practiced task, with no transfer to the untrained activity.

Regarding hand function, Trumbower et al. reported significant improvements in both gross and fine manual dexterity after acute intermittent hypoxia combined with a hand-opening task.[12] In contrast, Sandhu et al. found improvements only in gross dexterity after a single session of acute intermittent hypoxia without additional task-specific training.[25] This discrepancy may be due to the broader neural activation achieved when combining acute intermittent hypoxia with task-specific tasks, as in Trumbower et al.'s study, while acute intermittent hypoxia alone, as in Sandhu et al., likely engaged circuits involved in gross movements but not fine motor control.[39]

Four included studies reported improvements in upper extremity muscle strength and activity following acute intermittent hypoxia.[12, 23, 25, 27] These results may reflect changes in synaptic connections within the spinal cord, leading to peripheral improvements in muscle function. This can be expected as muscle impairments (such as atrophy, spasticity) following spinal cord injury are often linked to maladaptive neural plasticity within the spinal cord.[40] Moreover, improvements in hand dexterity and gait function through enhanced neural plasticity may indirectly support muscle function via increased active movement.

Our findings suggest with low to very-low evidence that acute intermittent hypoxia can enhance motor function in individuals with incomplete spinal cord injury. Acute intermittent hypoxia may be considered as an adjunctive therapy to complement physio- and occupational therapy, potentially allowing for increased neuroplasticity. Its potential benefits

in strengthening weakened muscles, improving hand function, balance and walking abilities could support more functional independence. Future clinical programs should consider integrating acute intermittent hypoxia with intensive task-specific practice. Careful monitor during acute intermittent hypoxia sessions, particularly in individuals with cardiovascular or respiratory vulnerabilities, is critical to avoid adverse effects.

Future research should focus on several key areas to optimise the understanding and application of acute intermittent hypoxia. Firstly, there is a need to standardise the intervention protocols, particularly in terms of duration, frequency, and intensity, as well as to define the specific content of acute intermittent hypoxia combined with motor training. Moreover, adherence to the acute intermittent hypoxia protocol and cost-effectiveness should be carefully evaluated to determine the feasibility of implementing this therapy in routine clinical practice. Future randomized controlled trials should aim to compare acute intermittent hypoxia interventions to the best available evidence and ensure that the dose and duration of the intervention are consistent across all groups. Future studies should also explore the combined effects of acute intermittent hypoxia and other rehabilitation strategies to determine the most effective treatment combinations for improving motor function and functional independence in individuals with incomplete spinal cord injury. Lastly, understanding the dose-response relationship, particularly in terms of optimal acute intermittent hypoxia exposure, will be crucial to maximize the benefits and guide clinical recommendations.

This work has several limitations. First, while different methods were used to be as exhaustive as possible, the limited number of randomized controlled trials included in the work weakens the overall certainty of the evidence. Further high quality and large randomized controlled trials are thus necessary. Second, since less than ten studies were included per forest-plots, we were not able to assess small study effects through funnel plots (indicative of potential publication biases).

In conclusion, this review, involving 9 randomized controlled trials, suggests with low to very low certainty of evidence that acute intermittent hypoxia is a safe intervention for individuals with incomplete spinal cord injury. The findings indicate that acute intermittent hypoxia can improve walking speed, endurance, muscle strength, and manual dexterity, highlighting its potential to enhance motor function and activity levels. However, no significant effect was observed on balance outcomes. Future studies with larger sample sizes and standardized protocols are needed to confirm these benefits.

Ethical considerations

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Declaration of conflicting interests

The authors report there are no competing interests to declare.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

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Tables

Table 1. Search strategies

PubMed	("intermittent hypoxia"[Title/Abstract] OR "intermittent hypoxic therapy"[Title/Abstract] OR "intermittent hypoxic training"[Title/Abstract] OR "intermittent hypoxia-hyperoxia"[Title/Abstract]) AND ("spinal cord"[MeSH Terms] OR "spinal cord injuries"[MeSH Terms] "cord injury"[Title/Abstract] OR "spinal cord trauma"[Title/Abstract] OR "spinal neuropathy"[Title/Abstract] OR "cervical cord injury"[Title/Abstract] OR "cervical cord trauma" [Title/Abstract] OR "SCI" [Title/Abstract])
Embase	('spinal cord injury'/exp OR 'injury, spinal cord' OR 'spinal cord injuries' OR 'spinal cord injury' OR 'spinal cord trauma' OR 'trauma, spinal cord' OR 'cervical spinal cord injury'/exp OR 'cervical cord injury' OR 'cervical cord lesion' OR 'cervical spinal cord injury' OR 'cervical spinal cord lesion' OR 'cervical spinal cord trauma' OR 'cervical spine cord lesion' OR 'injury, cervical spinal cord' OR 'injury, spinal cord, cervical' OR 'spinal cord injury, cervical' OR 'trauma, cervical spinal cord' OR 'trauma, spinal cord, cervical') AND ('intermittent hypoxia'/exp OR 'intermittent hypoxia' OR 'intermittent hypoxic training'/exp OR 'hypoxia interval training' OR 'hypoxic interval training' OR 'intermittent hypoxia therapy' OR 'intermittent hypoxia training' OR 'intermittent hypoxic exercise' OR 'intermittent hypoxic therapy' OR 'intermittent hypoxic training' OR 'interval hypoxia training' OR 'interval hypoxic exercise' OR 'interval hypoxic training')
Scopus	(TITLE-ABS-KEY("intermittent hypoxia" OR "intermittent hypoxic therapy" OR "intermittent hypoxic training" OR "intermittent hypoxia-hyperoxia")) AND (TITLE-ABS-KEY("spinal cord injur*" OR "spinal cord trauma" OR "spinal neuropathy" OR "cervical cord injur*" OR "cervical cord trauma" OR "SCI"))
Cochrane Library	Title Abstract Keyword: "intermittent hypoxic training" OR "intermittent hypoxia" OR "intermittent hypoxic therapy" OR "intermittent hypoxia-hyperoxia" AND Title Abstract Keyword: "spinal cord injury" OR "spinal cord trauma" OR "cervical cord trauma" OR "spinal neuropathy" OR "cervical cord injury" OR "SCI"

Table 2. Characteristics of included studies

Authors	Experimental intervention	Control intervention	Mean age (min – max)	N (F/M)	ASIA Grade	Time since diagnosis (years)	Country
Afsharipour et al., 2023[23]	One 30 min session of AIH with 15 x 60s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2	One 30 min session of sham AIH with 15 x 60s of 21% 0_2 interleaved with 15 x 60s of 21% 0_2	48.1 (21 – 65)	7 (2/5)	C-D	7	USA
Hayes et al., 2014[11]	Block 1: 30 min session of AIH with 15 x 60s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2 for 5 consecutive days Block 2: 30 min session of AIH with 15 x 60s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2 + 30 min of walking overground at maximal sustainable exertion; during 5 consecutive days	Block 1: 30 min session of sham AIH with 15 x 60s of 21% 0_2 interleaved with 15 x 60s of 21% 0_2 for 5 consecutive days Block 2: 30 min session of sham AIH with 15 x 60s of 21% 0_2 interleaved with 15 x 60s of 21% 0_2 + 30 min of walking overground at maximal sustainable exertion; during 5 consecutive days	43 (24 – 77)	24 (3/21)	C-D	9	USA
Opazo et al., 2017 (a)[14]	45 min session of AIH with 15 x 90s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2 + 45 min of body weight-supported treadmill training; during 5 consecutive days the first week and three times per week for the next three weeks (total duration = 4 weeks)	45 min session of continuous normoxia (21% 0_2) + 45 min of body weight-supported treadmill training; during 5 consecutive days the first week and three times per week for the next three weeks (total duration = 4 weeks)	41 (19 – 71)	35 (4/31)	C-D	4	Chile
Opazo et al., 2017 (b)[13]	45 min session of AIH with 15 x 90s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2 + 45 min of body weight-supported treadmill training; during 5 consecutive days the first week and three times per week for the next three weeks (total duration = 4 weeks)	45 min session of continuous normoxia (21% 0_2) + 45 min of body weight-supported treadmill training; during 5 consecutive days the first week and three times per week for the next three weeks (total duration = 4 weeks)	41 (19 – 71)	35 (4/31)	C-D	4	Chile
Opazo et al., 2017 (c)[24]	45 min session of AIH with 15 x 90s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2 + 45 min of body weight-supported treadmill training; during 5 consecutive days the first week and three times per week for the next three weeks (total duration = 4 weeks)	45 min session of continuous normoxia (21% 0_2) + 45 min of body weight-supported treadmill training; during 5 consecutive days the first week and three times per week for the next three weeks (total duration = 4 weeks)	41 (19 – 71)	35 (4/31)	C-D	4	Chile
Sandhu et al., 2021[25]	Block 1: One 30 min session of AIH with 15 x 60s of 9% 0_2	Block 1: One 30 min session of sham AIH with 15 x 60s of 21%	46.9 (23 - 64)	18 (2/16)	C-D	>0.5	USA

	interleaved with 15 x 60s of 21% 0_2 Block 2: 30 min session of AIH with 15 x 60s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2 during 2 consecutive days	0_2 interleaved with 15 x 60s of 21% 0_2 Block 2: 30 min session of sham AIH with 15 x 60s of 21% 0_2 interleaved with 15 x 60s of 21% 0_2 during 2 consecutive days					
Tan et al., 2021[26]	37.5 min session of AIH with 15 x 90s of 10% 0_2 interleaved with 15 x 60s of 21% 0_2 + 30 min of walking at maximal voluntary speed; during 5 consecutive days	37.5 min session of sham AIH with 15 x 90s of 21% 0_2 interleaved with 15 x 60s of 21% 0_2 + 30 min of walking at maximal voluntary speed; during 5 consecutive days	46.8 (20 – 68)	11 (2/9)	C-D	8.5	USA
Trumbower et al., 2012[27]	Block 1: One 30 min session of AIH with 15 x 60s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2 Block 2: One 37.5 min session of AIH with 15 x 90s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2	Block 1: One 30 min session of sham AIH with 15 x 60s of 21% 0_2 interleaved with 15 x 60s of 21% 0_2 Block 2: One 37.5 min session of sham AIH with 15 x 90s of 21% 0_2 interleaved with 15 x 60s of 21% 0_2	46 (26-61)	13 (1/12)	C-D	10	USA
Trumbower et al., 2017[12]	37.5 min session of AIH with 15 x 90s of 9% 0_2 interleaved with 15 x 60s of 21% 0_2 + 20 repetitions of hand opening practice	37.5 min session of sham AIH with 15 x 90s of 21% 0_2 interleaved with 15 x 60s of 21% 0_2 + hand opening practice	43 (28 – 56)	6 (0/6)	C-D	19	USA

AIH = Acute IH; ASIA = American Spinal Injury Association Impairment Scale.

Table 3. Reported outcomes, funding and conclusions of included studies

Authors	Outcomes	Study funding	Conclusion
Afsharipour et al., 2023[23]	• Safety - HR - Systolic blood pressure - Oxyhaemoglobin saturation • Muscular strength during maximal voluntary elbow flexion and extension • Muscle activity during maximal voluntary elbow flexion and extension • Area of the active region during maximal voluntary elbow flexion and extension	National Institute on Disability, Independent Living, and Rehabilitation Research training grant and a NIDILRR Midwest Regional SCI Model System grant	Strength and spatial distribution of EMG activity in people with iSCI's upper limb proximal muscles increase following a single session of AIH.
Hayes et al., 2014[11]	• Safety - Serious and non-serious adverse events - Oxyhaemoglobin saturation - HR - Arterial blood pressure - Motor and cognitive functions using the SCATS, LE-ASIA, SCIM, MMSE • Walking speed with the 10MWT • Walking endurance with the 6MWT • Walking quality with the WISCIFAI	US Department of Defense Spinal Cord Injury Research Program grant	Daily AIH combined with walking training improves walking speed and distance in persons with chronic iSCI.
Opazo et al., 2017 (a)[14]	• Safety - Serious and non-serious adverse events - Oxyhemoglobin saturation - Oxygen concentration during the hypoxic episodes • Standing balance (instrumented sway measures) • Dynamic balance (instrumented TUG test measures)	Fondecyt Grant, National Commission of Scientific and Technological Research, Chile	A 4-week protocol of AIH associated with walking training enhances dynamic, but not standing balance in people with iSCI
Opazo et al., 2017 (b)[13]	• Safety - Serious and non-serious adverse events - Oxygen concentration during the hypoxic episodes - Pain intensity with a VAS - Spasticity with the AS • Walking speed with the 10MWT • Walking endurance with the 6MWT	Fondecyt Grant, National Commission of Scientific and Technological Research, Chile	Five consecutive days of AIH combined with walking training improve walking speed and endurance in subjects with iSCI.
Opazo et al., 2017 (c)[24]	• Safety - Serious and non-serious adverse events - Oxygen concentration during the hypoxic episodes	Fondecyt Grant, National Commission of Scientific and Technological Research, Chile	A 4-week protocol of moderate IH does not elicit visual or verbal memory impairment

	- Episodic verbal memory with the TAVEC - Episodic visual memory with the ROCF		
Sandhu et al., 2021[25]	• Grip strength • Pinch strength • Gross manual dexterity with the BBT • Fine manual dexterity with the NHPT	U.S. Department of Health and Human Services, Administration on Community Living, National Institute on Disability, Independent Living and Rehabilitation Research	A single AIH session can enhance upper limb function, as well as pinch and grasping strength, in persons with cervical iSCI.
Tan et al., 2021[26]	• Safety - Serious and non-serious adverse events - Oxyhaemoglobin saturation - HR - Systolic blood pressure • Walking speed with the 10MWT • Walking endurance with the 6MWT • Kinematics of the trunk and less-affected leg during gait cycles • Intralimb coordination (cycle-by-cycle variability in footpath trajectories and interjoint angular displacements of the more affected leg)	Wings for Life Foundation, The United States Department of Defense, the National Institutes of Health, and the Craig H. Neilsen Foundation	Five consecutive days of AIH combined with walking improve walking performance in persons with chronic iSCI.
Trumbower et al., 2012[27]	• Safety - Oxyhaemoglobin saturation - HR • Voluntary ankle strength (using torque generation and EMG activity)	Craig H. Neilsen Foundation	AIH seems to offer increases in volitional somatic motor output in persons with chronic iSCI.
Trumbower et al., 2017[12]	• Safety - Serious and non-serious adverse events - Oxyhaemoglobin saturation - HR - Blood pressure - Cognitive function using the MMSE • Gross manual dexterity with the BBT • Hand use during ADL with the JTHT • Hand maximal opening using optical motion analyses systems • Changes in muscle coordination during maximum opening (using EMG activity)	Craig H. Neilsen Foundation and NIH NINDS	Daily AIH combined with hand opening practice may improve hand function in persons with chronic iSCI

AS = Ashworth Scale; AIH = Acute Intermittent Hypoxia; BBT = Box and Block Test; EMG = Electromyography; HR = Heart Rate; iSCI = incomplete Spinal Cord Injury; LE = Lower Extremity; MMSE = Mini Mental State Examination; NHPT = Nine Hole Peg Test; ROCF = Rey-Osterrieth Complex Figure Test; SCATS = Spinal Cord Assessment Tool for Spasticity; SCI = Spinal Cord Injury; SCIM = Spinal Cord Independence Measure; TAVEC = Spanish Complutense verbal learning test; TUG = Timed-Up and Go; VAS = Visual Analog Scale; WISCIFAI = Walking Index for Spinal Cord Injury and Spinal Cord Injury Functional Ambulation Inventory 10MWT = Ten Meter Walk Test; 6MWT = 6-Minute Walk Test.

Table 4. Summary of findings

Intermittent hypoxia compared with sham intermittent hypoxia for incomplete spinal cord injury rehabilitation			
Population: People with incomplete spinal cord injury **Settings:** Hospital, clinic or home **Intervention:** Acute intermittent hypoxia (paired or not with motor training) **Comparison:** Sham intermittent hypoxia (paired or not with motor training)			
Outcome	**Effect size and direction of effect (95% CI)**	**Number of participants (studies)**	**Certainty of the Body of Evidence**
Treatment adherence	**1. AIH alone** No significant difference found on treatment adherence: RD = 0.08 (-0.11 – 0.26) **2. AIH + gait training** No significant difference found on treatment adherence: RD = 0.04 (-0.11 – 0.18) **3. AIH + hand opening practice** No significant difference found on treatment adherence: RD = 0.00 (-0.46 – 0.46)	1. 46 (4) 2. 57 (3) 3. 6 (1)	Low[a,b]
Walking speed	**AIH + gait training** Significant difference found in favour of AIH: MD = 5.97 (1.4 – 10.54)	53 (3)	Low[a,b]
Walking endurance	**AIH + gait training** Significant difference found in favour of AIH: MD = 39.48 (2.32 – 76.63)	54 (3)	Very low[a,b,d]
Balance	**AIH + gait training** No significant difference in normalized jerk and root mean square of sway. Significant improvement in turning duration, turn-to-sit duration, and steps during a turn.	33 (1)	Very low[a,c]
Muscle strength and activity	**1. AIH alone** Significant improvement in elbow flexion/extension strength and activity and ankle plantar flexion strength. **2. AIH + hand opening practice** Significant improvement in maximum hand aperture and hand muscle EMG activity	1. 38 (3) 2. 6 (1)	Low[a,b]
Manual dexterity	**1. AIH alone** Significant improvement in Box and Block Test but no significant effect on Nine Hole Peg Test. **2. AIH + hand opening practice** Significant improvement in Box and Block Test scores	1. 18 (1) 2. 6 (1)	Low[a,b]

[a] = Downgraded one level due to Risk of Bias in included studies' overall Risk of Bias; [b] = Downgraded one level due to imprecision related to small sample size; [c] = Downgraded by two levels as only one study provided results for this outcome; [d] = Downgraded one level due to inconsistency related to considerable between-studies statistical heterogeneity; AIH = Acute intermittent hypoxia; n = number of participants; N = number of trials; RCT = randomized controlled trial.

Supplementary Material

Supplementary File 1. Risk of Bias

Figures

Figure 1. Flow chart diagram

Figure 2. Forest plot representing the risk difference of dropping out between AIH and sham AIH

Figure 3. Forest plot representing the effect of AIH combined with gait training on walking speed.

Figure 4. Forest plot representing the effect of AIH combined with gait training on walking endurance.