Safety and efficacy of prone positioning in mechanically ventilated adult patients with acquired brain injury: a narrative systematic literature review

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Abstract

Background: Prone positioning has proven clinical benefit in ARDS patients. There is clinical dilemma in patients at risk of respiratory failure with concurrent brain injury and reduced intracranial compliance who may benefit from prone positioning. Current guidelines are lacking evidence and recommendations regarding management in context of this clinical scenario.

Objectives: This study aimed to determine the safety and efficacy of prone positioning in mechanically ventilated adult patients with acquired brain injury using a narrative systematic review.

Methods: The following databases were searched: CENTRAL, MEDLINE, Cochrane, ClinicalTrials.gov, HERDIN for relevant studies from the last 20 years. Prespecified screening and eligibility criteria for inclusion were applied. Included studies underwent methodological quality assessment. Study design, patient characteristics, interventions given, and relevant outcomes were extracted and summarized.

Results: This review included five relevant articles – 1 randomized controlled trial (RCT) and 4 observational studies (2 retrospective case-series, 2 prospective case-series). There was a total of 114 patients included in the studies (51 from the RCT and 63 from the observational studies). The RCT was found to be of fair methodological quality, while the 4 observational studies satisfied most of the criteria of good methodological quality based on risk of bias assessment tools used. General consensus revealed improved oxygenation in mechanically ventilated ABI patients with Level 4 evidence, but may increase ICP levels with Level 2 evidence at most.

Conclusion: It may be safe and effective in a carefully selected population of mechanically ventilated ABI patients if ICP monitoring is available.

Keywords: Prone Positioning; Intracranial Pressure; Mechanical Ventilation; Acquired brain injury; Systematic Review

Abbreviations:

ABI – acquired brain injury
ARDS – acute respiratory distress syndrome
CENTRAL – Cochrane Central Register of Controlled Trials
CPP – cerebral perfusion pressure
GCS – Glasgow coma score
HERDIN – Health Research and Developmental Information Network of the Philippines
ICP – intracranial pressure
LIS - lung injury score
MAP – Mean arterial pressure
MeSH – medical subject headings
$PaCO_2$ – arterial partial pressure of carbon dioxide
PaO_2 – arterial partial pressure of oxygen
PEEP – positive end-expiratory pressure
PF – PaO_2/FaO_2

PP – prone positioning
PRISMA – Preferred Reporting Items for Systematic reviews and Meta-analyses
PROSEVA - Prone Positioning in Severe Acute Respiratory Distress Syndrome
$ptiO_2$ – brain tissue oxygen partial pressure
RCT – randomized controlled trials
SP – supine positioning
SaO_2 – arterial oxygen saturation

1. Introduction

During the initial phase of brain injury, tissue deformation occurs that causes varying irreversible damage to neurons, glia, axons, and blood vessels. This is followed by a more delayed phase of injury mediated by biologic pathways in the cellular level which can be present for minutes and persistently up to weeks after primary injury. In this delayed phase, many patients experience secondary insults such as hypoxia, hypotension, cerebral swelling, and consequences of increased intracranial pressure (ICP) (Shahlaie et al., 2017) [1]. Arterial hypotension, reduced cerebral perfusion pressure, elevated ICP and hypoxemia have been consistently correlated with poor clinical outcome (Jones et al., 1994) [2]. Several studies on acute brain injury (ABI) focus on preventing or lessening the extent of secondary injury by managing intracranial hypertension, and maintaining adequate oxygenation.

Mechanical ventilation is often necessary in patients with ABI, especially those presenting with profound alterations in sensorium; and respiratory deterioration can be multi-etiological (Dela Torre et al., 2017) [3]. Additionally, acute respiratory insufficiency is the most common non-neurological organ dysfunction in severe traumatic brain injury with a major impact on outcome (Zygun et al., 2005) [4]. In brain-injured patients with reduced intracranial compliance, coexistence of respiratory failure depicts a poor clinical picture and ventilatory management can be very challenging, as ventilatory targets are often in conflict in these two conditions and lung protective ventilatory strategies are associated with an increased risk of intracranial hypertension and varying effects on cerebral perfusion (Dela Torre et al., 2017) [3].

Therapeutic prone positioning (PP) is one of those strategies which has been subject to a number of studies. In the past 20 years, five major trials have tried to demonstrate the effectiveness of prone position as supportive therapy for acute respiratory distress syndrome (Gattinoni et al., 2001, Guérin et al., 2004, Mancebo et al, 2006, Taccone et al., 2009, Guérin et al., 2013) [5,6,7,8,9] Of these studies, the Prone Positioning in Severe Acute Respiratory Distress Syndrome (PROSEVA) trial, a large multicenter prospective randomized study showed a significant reduction of mortality after 28 and 90 days in acute respiratory distress syndrome (ARDS) patients treated with prone positioning compared to supine positioning (Guérin et al., 2013) [9] However, all those major trials have excluded patients with ABI.

There is a scarcity of available data to evaluate the benefits and risks of prone positioning in patients with ABI. This paper aimed to review available literature on this subset of patients in order to obtain more insight into the influence of prone position on ICP and oxygenation in the intensive care unit (ICU) setting.

In this review, the term ABI was used to refer to acquired brain injuries which is any damage to the brain that occurs after birth and is not related to a congenital or a degenerative disease, and could be from external or internal causes. This operational definition was used to be as inclusive as possible to studies which involve brain injury from traumatic and non-traumatic causes.

2. Methods

This study adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Guidelines [10].

2.1. Criteria for selection of studies

The author considered randomized controlled trials (RCT); prospective/retrospective cohort studies; and case series. Adult patients with ABI who were mechanically ventilated, placed on PP and subjected to ICP monitoring were the main prerequisites of including studies. Additionally, reported baseline and post-intervention measures of ICP and respiratory

parameters were a must for the included studies. Studies were chosen regardless of etiology of ABI, baseline neurologic status of the study population, and existing pulmonary pathology of the study population. Studies with concurrent lung protective ventilatory strategies as seen required by patients other than PP were included.

2.2. Primary and secondary outcomes

The primary outcome for this review was ICP levels measured as mean level during and/or after PP; and arterial oxygen partial pressure (PaO_2) levels measured as mean level during and/or after PP.

Secondary outcomes included: 1) PaO_2/FaO_2 (PF) ratio, 2) arterial oxygen saturation (SaO_2), 3) arterial partial pressure of carbon dioxide ($PaCO_2$), 4) cerebral perfusion pressure (CPP), and 5) mean arterial pressure (MAP)

2.3. Search methods for identification of studies

Literature search using medical subject headings (MeSH) and free texts related to ("prone") AND ("intracranial pressure") were used. Time frame limit was set to retrieve articles in the last 20 years with English full-text document available. The following databases were systematically searched: Medline (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov website, and Health Research and Development Information Network (HERDIN) of the Philippines. Citations of the selected studies were also searched for relevant studies.

Primary screening involved reviewing the titles and abstracts of the available studies. Full-text articles were obtained for relevant studies and secondary screening allowed the author to select the studies that satisfied that predefined eligibility criteria to be included in this review.

2.4. Risk bias assessment, data collection, and analysis

Risk of bias was assessed for each included study. The Cochrane Collaboration Tool was used for RCTs. For observational studies, the tool developed by Murad et al., 2018 [11] was used to assess for bias, which comprises eight questions categorized into four domains: selection, ascertainment, causality, and reporting – all of which were critical to determine risk of bias in context of this review's objective.

Year publication, study design, population size and mean age, details of PP as intervention used, measures of intracranial and respiratory parameters pre and post intervention, and adverse events related to PP were extracted from each included study. The author narratively summarized current knowledge reflected in the literature, and level of evidence was generated as adapted from a method used by Meyer et al., 2010 [12]:

- Level 1 evidence: Findings supported by the results of one or more RCT of at least good quality
- Level 2 evidence: Findings supported by a single RCT of at least fair quality
- Level 3 evidence: Findings supported by at least one case-control study
- Level 4 evidence: Findings supported by at least one: a) Pre–post-test: A prospective trail with a baseline measure and a post-intervention measure in a single group of subjects; b) Post-test: A prospective study using a post-intervention measure only (no pre-test or baseline measurement with one or more groups); c) Case series: A retrospective study, usually a chart audit.
- Conflicting evidence: Findings are in direct contradiction in at least two papers of similar methodological quality.

3. Results

3.1. Included studies

As shown in Figure 1, identification, screening, and application of eligibility criteria to relevant studies were done. Of all the mentioned databases searched, only PubMed yielded results wherein 96 articles were identified. Review of citations yielded 1 significant study. Screening of titles and abstracts was done for 97 records from which 90 were excluded mainly due to non-relevance to the study topic and absence of English full-text copy. Full-text articles for 6 studies were obtained and evaluated for eligibility. One study was excluded on the basis that it involved patients with no ABI who were for spinal surgery subjected to non-invasive ICP estimations (Robba et al., 2017) [13].

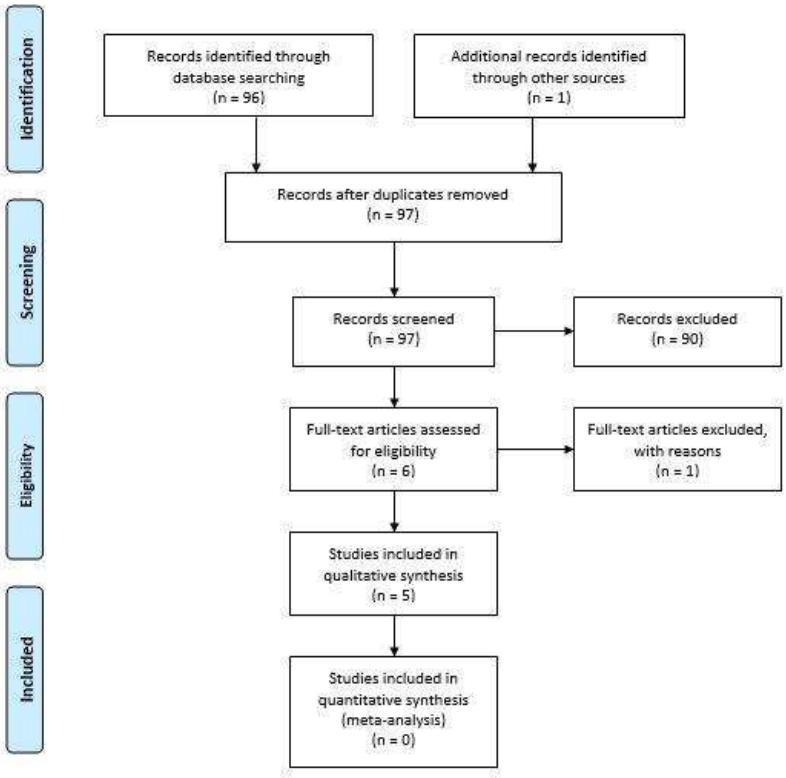

Figure 1. Flow diagram of the literature screening process as adapted from PRISMA guidelines [10]

3.2. Study design and patient population

Five studies satisfied the eligibility criteria (Beuret et al., 2002 [14]; Reinprecht et al., 2003 [15]; Thelandersson et al., 2006 [16]; Nekludov et al., 2006 [17]; Roth et al., 2014 [18]. All were published in international journals. Table 1 is a summary of patient characteristics, design, and methodology of included studies.

These studies were of different designs - 1 RCT (Beuret et al., 2002) [14], 2 retrospective case series (Reinprecht et al., 2003, Roth et al., 2014) [15,18], and 2 prospective case series (Thelandersson et al., 2006, Nekludov et al., 2006) [16,17]. All had different inclusion criteria but all studies involved mechanically ventilated ABI patients. Only one study included ARDS patients in its study population (Reinprecht et al., 2003) [15]. There was a total of 114 patients identified collectively in all studies – 51 patients from the RCT (25 in the PP group and 26 in the SP group), and 63 patients from the observational studies.

All studies utilized invasive ICP monitoring on all their patients, except the RCT which only 23% of enrolled had ICP monitoring (6 out of 25 patients in the PP group and 6 out of 26 patients in the SP group) (Beuret et al., 2002) [14]. Method of recording of ICP levels also differed on all the studies. These are again summarized on Table 1, including how they measured ventilation parameters for each patient.

Baseline neurologic status was not similar for all the studies. Beuret et al., 2002, enrolled patients who were Glasgow coma score (GCS) 9 or below [14]. The case series of Reinprecht et al., 2003 involved patients with subarachnoid hemorrhage, Hunt-Hess grades III-V [15]. Nekludov et al., 2006 studied patients treated at the intensive care unit for severe traumatic brain injury and subarachnoid hemorrhage with GCS 8 or below [17]. Thelandersson et al., 2006 and Roth et al., 2014, did not mention the baseline neurologic status of their patients [16, 18].

The manner of PP also varied in all the studies. These are simplified and summarized in Table 1. Beuret et al., 2002 did continuous cycles of PP 4 hours daily, until the patient is able to get up and sit in an armchair. If ICP increased over 30mm Hg, PP was stopped and the patient was returned to SP [14]. Reinprecht et al., 2003 placed patients in PP for 14 hours if

well tolerated. They were returned to SP earlier if ICP continuously exceeded 25mm Hg. In those patients who tolerate PP well, repeated cycles were performed as long as pulmonary function could be improved [15]. Thelandersson et al., 2006, placed patients in PP for 3 hours, then back to SP. Indications to return patient back to SP early include: ICP more than 20mm Hg and CPP less than 60mm Hg [16]. Nekludov et al., 2006, utilized a Stryker frame, which can be rotated 180 degrees, shifting from supine to prone and back again. The entire bed was sloped, with head of patient 10 degrees upward, regardless if in SP or PP. Treatment in PP was done for 1 hour [17]. Roth et al., 2014, placed patients in a 135-degree PP. If well tolerated, they stay in PP for 8 hours. If the respiratory situation was still unsatisfactory, another unit of PP was initiated [18].

All studies aimed to looked into the safety and efficacy of PP in terms of its effects on ICP and oxygenation in patients with ABI, except for Beuret et al., 2002, whose RCT's objective was to determine whether PP would prevent lung worsening in comatose patients which was evaluated by daily measurements of the Lung Injury Score (LIS) [14].

Table 1. Design, inclusion criteria, population characteristics, details of prone positioning, and outcome measures of included studies.

			Population		Details of prone positioning		Outcome Measures of interest		
Study	**Design**	**Inclusion**	**Size**	**Age (Mean)**	**Duration**	**Manner**	**ICP Measurements (h = hour)**	**Ventilation parameters**	**Clinical Outcome**
Beuret et al., 2002 [14]	Prospective, Randomized Controlled Study	Required invasive mechanical ventilation due to coma (GCS ≤9)	51	55	4 hours once daily	Complete prone	Available in 23% of enrolled patients (SP, PP 1h, PP 2h, PP 3h, PP 4h, SPP)	PaO_2/FIO_2 trend over first 14 days in percentage of baseline values	Death at Day 28, Duration of mechanical ventilation, Duration of intensive care unit stay, Good neurologic outcome at 3 months
Reinprecht, et al., 2003 [15]	Retrospective case series	SAH diagnosed clinically and confirmed by imaging; b) ARDS and c) treatment by prone positioning Hunt-Hess III-V	16	44	up to 14 hours once daily	Complete prone with head midline or turned slightly laterally and elevated between 15 and 20°	ICP, MAP and CPP measured 4h before the first PP and continuing until 6h after return to the SP; comparison as mean values SP vs PP	PaO_2 every 2h and $ptiO_2$ continuously at 15sec intervals	None
Thelandersson, et al., 2006 [16]	Prospective case series Pre-Post Design	Mechanically ventilated patients with a minimum FiO2 of 0.4 and an intraventricular catheter placed to measure the ICP	12	51	3 hours once daily	Complete prone	SP baseline, PP 10min, PP 1h, PP 3h, SPP 10min, SPP 1h *including CPP and MAP	PaO_2, SaO_2, $PaCO_2$, measured in intervals same as ICP	None
Nekludov et al., 2006 [17]	Prospective case series Pre-Post design	Adult patients treated at the ICU for severe traumatic brain injury, or subarachnoid hemorrhage, presenting with a GCS ≤8 with associated pulmonary pathology	8	53	1 hour once daily	Stryker frame with head of bed elevated at 10° regardless if SP or PP	SP baseline, PP 1h, SPP 1h *including CPP and MAP	PaO_2, SaO_2, $PaCO_2$, measurement taken once during baseline and twice during PP	None
Roth et al., 2014 [18]	Retrospective Study	Patients with severe intracranial pathologies who were treated with kinetic therapy for at least one treatment unit of prone positioning and concurrent monitoring of intracerebral pressure	29; analyzed as 119 treatment units	57	up to 8 hours once daily	135° prone position	ICP and CPP continuously recorded every hour regardless of position	PEEP, $PaCO_2$, PaO_2/FIO_2) were documented before, during and the day after the last movement of a patient to a prone position	None

3.3. Methodological quality assessment

Bias was evaluated using the Cochrane Collaboration's tool for the RCT of Beuret, et al, 2002. This RCT was rated a fair level of methodological quality as seen in table 2.

Table 2. Risk of bias summary using the Cochrane Collaboration's tool for RCTs

Bias domain	Source of bias	Support for judgement	Author's judgement
Selection bias	Random sequence generation	Method of randomization was not specified. The study just mentioned that the patients were randomized into SP and PP group from a pool of patients that specified the eligibility criteria. Although they presented that the baseline characteristics of patients from the two groups at randomization were similar.	Unclear Risk
	Allocation concealment	Further description of allocation is not included	Unclear Risk
Performance bias	Blinding of participants and personnel	Comatose patients could not have known they were included in a study. A physician blinded to the study reviewed chest x-rays to verify that the new radiographic infiltrate was not present at the time of intubation. (Primary endpoint of the study was incidence of lung worsening defined by an increase in the LIS of at least 1 point since time of randomization computed using values of PF ratio, PEEP and X-ray grading.)	Low Risk
Detection bias	Blinding of outcome assessment	Comatose patients were enrolled in the study	Low Risk
Attrition bias	Incomplete outcome data	Losses to follow-up were disclosed for which there were none. Data were analyzed on an intention-to-treat basis but not all 53 patients initially randomized were included in the analysis. 2 patients from the SP group died in the first 24 hours. This is a reasonable attrition and not expected to significantly affect results. Adequate sample size of 33 patients per group was not achieved.	Unclear Risk
Reporting bias	Selective Reporting	All prespecified outcomes were reported	Low Risk
Other bias		None identified	

For the four included observational studies, bias was assessed using the tool proposed by Murad et al., 2018, presented in table 3[11]. These studies did not rule out other alternative causes that may explain the observation. Although some studies used concurrent ventilatory strategies aside from PP; they were only instituted as necessary or kept within institutional protocol, hence there is no way to fully verify whether these additional interventions could have had a significant effect on the observed outcome, likewise can be said for the use of ICP lowering medication which was claimed to be kept well within baseline across the study population. There was no challenge/re-challenge done in any of the studies. Dose/exposure-response effect was not manifested in the studies except for the study of Thelandersson et al., which presented outcome data in relation to different time points of prone positioning (e.g. 3 hours in PP reflected better values of ventilation status as compared to the 10-minute and 1-hour time points). Th remaining questions were satisfied by all four studies. Therefore, all observational studies satisfactorily addressed the necessary aspects for good methodological quality.

Table 3. Risk of bias assessment for included observational studies

Domains	Leading Explanatory Questions	Reinprecht 2003	Thelandersson 2006	Nekludov 2006	Roth 2006
Selection	1. Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	Clear Selection Method	Clear Selection Method	Clear Selection Method	Clear Selection Method
Ascertainment	2. Was the exposure adequately ascertained?	Yes	Yes	Yes	Yes
	3. Was the outcome adequately ascertained?	Yes	Yes	Yes	Yes

Causality	4. Were other alternative causes that may explain the observation ruled out?	No	No	No	No
	5. Was there a challenge/rechallenge phenomenon?	No	No	No	No
	6. Was there a dose/exposure–response effect?	No	Yes	No	No
	7. Was follow-up long enough for outcomes to occur?	Yes	Yes	Yes	Yes
Reporting	8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	Yes	Yes	Yes	Yes

3.3. Effects of prone positioning

Beuret et al., 2002 [14]: In this RCT, 13 out of 26 (50%) patients presented lung worsening in the SP group compared to 3 out of 25 (12%) in the PP group (RR = 4.17; 95% CI =1.35-12.89; p= 0.003). Using survival analysis, 28-day lung worsening was lower in the PP group (p = 0.0018). Clinical outcomes (Death at day 28, duration of mechanical ventilation, duration of intensive care unit stay, good neurologic outcome at 3 months) were better for the PP group but not significantly different from the SP group. ICP monitoring was done only in 12 out of 51 (23%) patients, 6 patients for each PP and SP group. Mean values of ICP were recorded during 17 periods of PP. ICP levels (mean ± SD) were significantly elevated in PP at hours 1 (23.7 ± 9.6mm Hg), 2 (21.5 ± 4.3mm Hg), 3 (22 ±5.7mm Hg), 4 (20.2 ± 5.4mm Hg) as compared to baseline SP (11 ± 8.8mm Hg) ($p < 0.01$).

Reinprecht et al., 2003 [15]: In this case series, a significant increase in PaO_2 from 97.3 ± 20.7 torr (mean ± SD) in the SP to 126.6 ± 31.7 torr in the prone position was joined by a significant increase in brain tissue oxygen partial pressure ($ptiO_2$) from 26.8 ± 10.9 torr to 31.6 ± 12.2 torr (both $p < 0.0001$). whereas ICP increased from 9.3 ± 5.2mm Hg to 14.8 ± 6.7mm Hg and CPP decreased from 73.0 ± 10.5mm Hg to 67.7 ± 10.7mmHg (both $p < 0.0001$). There was no significant difference in MAP levels between the PP and SP.

Thelandersson et al., 2006 [16]: In this case series, there was a significant increase in PaO_2 measured at 3 hours in PP (SD ± mean) from 19.1 ± 6.1 kPa to 13.2 ± 2.1 kPa, 16.3 ± 6.5 kPa, 17.3 ± 6.5 kPa compared to baseline, 10 minutes in prone, and 1 hour in PP respectively ($p < 0.05$). SaO_2 levels were significantly increased in the PP as well. No significant changes were demonstrated in ICP, CPP, MAP, and $PaCO_2$.

Nekludov et al., 2006 [17]: In this case series, a significant improvement in PaO_2 was observed in the PP, from (mean ± SD) 12.6 ± 1.4 kPa to 15.7 ± 3.2 kPa ($p < 0.05$). Both ICP and MAP increased in PP, from 12 ± 6 to 15 ± 4mm Hg ($p < 0.05$), and from 78 ± 8 to 88 ± 8mm Hg ($p < 0.01$), respectively. Arterial pressure increased to a greater extent than ICP, resulting in improved CPP, from 66 ± 7 to 73 ± 8mm HG ($p < 0.05$) in PP.

Roth et al., 2014 [18]: In this case series, ICP increased significantly from (mean ± SD) 9.5 ± 5.9mm Hg to 15.4 ± 6.2mm Hg ($p < 0.0001$) in PP. Overall, an increase of mean ICP during PP was observed in 87.4% of all treatment units (n=104/119). MAP significantly decreased from 72.6 ± 17.5mm Hg in SP to 64.7 ± 17.5mm Hg in PP. There was no significant difference between CPP in a PP or SP. The baseline mean P/F ratio was 135.4 ± 43 with a significant improvement during PP (339.8 ± 93.6) and after termination of PP (345.8 ± 84.6). Mean $PaCO_2$ levels remained within normal limits.

3.4. Summary of results

Table 4. Summary of results of included studies in relation to prone positioning

		Primary Outcomes		Secondary Outcomes					
Study	**Design**	**ICP**	**PaO_2**	**SaO_2**	**MAP**	**CPP**	**P/F ratio**	**$PaCO_2$**	**Additional findings:**
Beuret et al., 2002	Prospective, Randomized Controlled Study	**(-)**	**0**	**0**	**0**	**0**	**0**	**0**	28 day lung worsening lower in PP group; clinical outcomes better in PP but not significant Pressure ulcer incidence PP=SP
Reinprecht et al., 2003	Retrospective case series	**(-)**	**(+)**	**0**	**ND**	**(-)**	**0**	**0**	(+) ptiO2 No adverse outcome reported
Thelandersson et al., 2006	Prospective case series	**ND**	**(+)**	**(+)**	**ND**	**ND**	**0**	**ND**	
Nekludov et al., 2006	Prospective case series	**(-)**	**(+)**	**0**	**(+)**	**(+)**	**0**	**0**	
Roth et al., 2014	Retrospective case series	**(-)**	**0**	**0**	**(-)**	**ND**	**(+)**	**ND**	
(+), beneficial result; (ND) no difference; (-), negative result; (0), no data									

Summary of results regarding the various effects of prone positioning on ICP, oxygenation, and other respiratory and hemodynamic parameters are presented in Table 4. Four out of 5 studies showed a general consensus that PP may increase ICP levels in mechanically ventilated patients with ABI with Level 2 (Meyer et al., 2010) [12] evidence at the most. This similar outcome appeared despite employment of different methods of PP by the included studies. Only the study by Thelandersson et al., 2006, showed that PP had no adverse effect on ICP level.

Oxygenation appeared to generally improve in all the observational studies in this subset of patients based on the different respiratory parameters collated from their outputs supported by Level 4 (Meyer et al., 2010) [12] evidence. Although, the RCT of Beuret et al., 2002, did not have data on respiratory parameters presented, their study showed good clinical outcomes (although non-significant) and lower 28-day lung worsening in patients in the PP group. Additionally, Reinprecht et al., 2003, presented a significant improvement in $ptiO_2$, which represents a more direct measure of cerebral brain tissue oxygenation.

Only 2 studies explicitly mentioned about adverse outcomes directly attributable to prone positioning unrelated to ICP elevation (Beuret et al., 2002, Reinprecht et al., 2003) [14,15]. The RCT found that the incidence of pressure ulcer of grade 2 or more, regardless of site of the lesion was similar in the PP and SP group. Reinprecht, et al. 2003, stated that aside from ICP elevations, no complications from PP were observed in their study.

4. Discussion

The 15 to 30-degree head elevation on supine is the ideal position for brain injured patients because it can significantly decrease ICP while maintaining CPP and cardiac output (Feldman et al., 1992) [19]. ICP decreases because on head elevation: 1) there is hydrostatic displacement of cerebrospinal fluid from the cranial cavity to the spinal subarachnoid space; and 2) venous outflow is facilitated. In contrast, prone positioning increases ICP through an increase in the cerebral venous pressure (Iwabuchi et al., 1983) [22]. In patients with increased ICP, such as in ABI, there is decreased intracranial compliance, whereby, smaller changes in intracranial volume will produce greater changes in ICP making proper positioning an important part in the standard of care. According to the most recent Brain Trauma Foundation Guidelines, evidence suggest that ICP levels above 22mm Hg is the threshold for treatment because pressure levels beyond this have been associated with an increase in mortality (Carney et al., 2017) [21].

Therapeutic prone positioning is used to improve oxygenation in mechanically-ventilated patients at risk of respiratory failure (Artigas et al., 1998) [23]. In fact, it has been shown to significantly reduce mortality in patients with ARDS, however, mortality benefit is seen in the subset of patients who have P/F ratio of 150 and below (Guérin et al., 2013) [9]. It is not useful as long-term therapy in patient with P/F ratio above 150 because their anatomic and clinical characteristics allow standard mechanical ventilation protocol to satisfy oxygenation requirements (Gattinoni et al., 2019) [24].

We are presented with great clinical dilemma if we encounter ABI patients at risk for respiratory failure whose oxygenation status may benefit from PP. This systematic review aimed to evaluate available literature regarding the safety

and efficacy of prone positioning in mechanically ventilated ABI patients, however it proved to be difficult because of the paucity of good studies even in widely known databases. A total of five studies were found – 1 RCT and 4 observational studies with a general consensus that PP in mechanically-ventilated ABI patients, ICP indeed is increased, but with significant improvement in oxygenation. Although there is apparent congruence in the results of these studies, much methodological heterogeneity (Table 1) prevents us from making a definite conclusion.

Only 1 study involved ARDS patients exclusively (Reinprecht et al., 2003) [15]. Mean duration of PP in the PROSEVA trial was 17 hours daily for 4 days – none of the studies was able to replicate this treatment duration. All of the studies had different treatment protocols, each having different termination criteria of treatment as well (Table 1). The mortality benefit as suggested by the PROSEVA trial is unlikely to be expected from the studies in this review.

Additionally, none of the included studies involved patients with ICP levels 20mm Hg or more at baseline likely because they have already been started on initial tier ICP lowering interventions per institution protocol. Therefore, a good clinical question for further studies to look into would be:" Will the mortality benefit of PP on respiratory status outweigh the possible mortality risk it poses on ARDS patients already presenting with significant refractory ICP elevations?".

Across all included studies in this review, inclusion criteria are encompassing of varying brain pathologies, which involve different pathophysiologic mechanisms. Although majority of their study population involved cases of traumatic brain injury, we are unable to say in which specific conditions PP will work best on based on current evidence. However, with this review, we are more or less given a general idea about the effect of PP in patients with reduced intracranial compliance with regards to oxygenation and ICP changes.

5. Conclusion

Is it effective? There is Level 4 evidence that PP improves oxygenation in mechanically ventilated patients with ABI. Good clinical outcomes have been reported but to a non-significant degree.

Is it safe? There is a general consensus among the studies that PP may increase ICP levels in mechanically ventilated patients with ABI with Level 2 evidence at the most. No adverse events directly attributable to PP unrelated to the expected ICP elevation were reported in 2 studies aside from occurrence of pressure ulcers.

The extent to how much PP increases ICP in those already with reduced intracranial compliance has not yet been answered, but it appears to be reasonable to do PP in severely hypoxemic ABI patients when other rescue therapies instituted have not been effective as long as strict ICP monitoring is present to maintain ICP levels 22mm Hg and below.

6. Recommendations

To be able to make more definite treatment guidelines, the authors believe that future researches should involve a more homogenous study inclusion criteria – possibly, patients with severe traumatic brain injury. Invasive ICP monitoring must be available in the institution conducting the study. Studies should include patients with baseline GCS scores of 3-8 with intact brainstem function provided that existing hydrocephalus or mass lesions have been addressed as needed. Patients should be clustered within a specific range of baseline ICP (e.g., 10-15mmHg, 15-20mmHg, 20-25mmHg) because intracranial compliance decreases with increasing ICP levels – a pathophysiologic mechanism which will have significant influence on treatment effect. We believe that the PP as described by Nekludov et al., 2006 [16], was the most ideal for this subset of patients which was, a 10-degree head of bed elevation regardless of whether in SP or PP, however, mortality benefit in ARDS patients has only been seen in complete prone position as proven by the PROSEVA trial. Treatment duration may vary and depend on the patients' ICP levels and oxygenation status. PP may be employed as long as ICP levels are kept at 22mm Hg and below, with termination of PP cycles as dictated by improvement of oxygenation status (e.g., P/F levels $\geq$ 150). ICP levels and ventilation parameters should be measured as mean values during SP and PP as seen similar to the study of Reinprecht et al., 2003 [15]. Lastly, we believe that $ptiO_2$ is an essential outcome measure to prove the benefit of PP in future studies because it is a more direct measure of brain tissue oxygenation.

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