Concussion Guidelines Step 1: Systematic Review of Prevalent Indicators

Supplemental Content 9
Analysis

The following section contains detailed analyses of the literature base for this report, organized in response to the four key questions.

Key Question 1 What are the most common signs, symptoms, and neurologic and cognitive deficits within three months following a potential concussive event?

SIGNS

Data Synthesis

Fourteen studies containing data about signs associated with a PCE met the criteria for this analysis and are included as evidence for this section.[1-14] Thirteen were studies of athletes; six samples were adults, four adolescents, and three mixed adult and adolescent subjects. The fourteenth study included adult and pediatric patients in a hospital environment.[5] A total of 1007 participants were assessed. In seven studies, 381 subjects served as their own controls with pre-injury baseline tests. Across six studies, 381 PCE subjects were compared to 212 controls, and for one study, 20 subjects both served as their own controls and were compared to 13 control subjects.

Results

LOC was reported in 13 studies; PTA in 7; RA in 6; AA in 2; disorientation/confusion in 3; and mental status change ≥ 5 min. in one study. In general, duration of LOC was not specified, but LOC > 30 min. was an exclusion criterion. PTA was either not specified, or dichotomized as “greater than” or “less than” a specified cut-point.

Prevalence of LOC across the included studies ranges from 1% to 39.3%; PTA from 2% to 29.7%; RA from 7.4% to 53.3%; AA from 1.6% to 57.1%; disorientation/confusion from 18% to 44.5%; and in the one study that reported mental status change ≥ 5 min., the prevalence was 18.4%; measures taken at or retrospectively recorded for immediately after injury.

Supplemental Content 10 shows the prevalence of signs across studies, and also includes information about each study’s sample characteristics, comparators, case definitions, and potential for bias details. This information is provided to assist in considering what factors might account for the disparity in the observed prevalence of signs. Supplemental Content 10 is organized based on prevalence of LOC, from least to most (the last publication, De Monte 2006,[5] did not report LOC).

There does not appear to be a pattern in the relationship between prevalence of LOC, sample size, and comparator type. Details of the assessment of potential for bias show high comparability across studies.

All studies reporting LOC except one have widely inclusive case definitions. Lovell et al[10] required that subjects have an abnormal score on at least one ImPACT module, and reports the second highest prevalence of LOC (21.4%). Two studies reporting the highest and third highest prevalence of LOC (39.3% and 20%) were conducted in Australia; one among Australian Rules football players,[11] and one among professional rugby league players.[6] It is possible that these factors (case definition and aggressiveness of sport) account for the high prevalence of LOC in these samples. As such, the upper boundary for signs prevalence for this report is set below the levels reported in these three studies.

At the other end of the spectrum are two studies that report the lowest prevalence of LOC; Kontos et al[8] reporting 1% in a sample of 96 high school and college athletes, and Covassin et al[4] reporting 3.8% in a sample of 79 college athletes. Given the lack of evidence for confounding factors that could account for the low LOC prevalence, the lower boundary for signs prevalence for this report includes these two studies.

Summary

Based on the available evidence, the following assertions have been derived:

Among athletes:

- LOC: prevalence ranges from 1% to 14.3%.
- PTA: prevalence ranges from 2% to 29.7%.
- RA: prevalence ranges from 7.4% to 53.3%.
- Disorientation/confusion: prevalence ranges from 18% to 44.7%.
- AA: given the limited number of studies reporting AA, there are insufficient data to make assertions about the prevalence of AA following a PCE.
- Mental Status Change > 5 min: given the limited number of studies reporting and mental status change $\geq$ 5 min., there are insufficient data to make assertions about the prevalence of these signs following a PCE.

Among hospital patients:

There are insufficient data to make assertions about the prevalence of signs following a PCE.

SYMPTOMS

One study containing data about symptoms following a PCE met the criteria for this analysis and is included as evidence for this section.[11]

Results

Seven symptoms (headache, dizziness, blurred vision, nausea, double vision, noise sensitivity, and light sensitivity) were measured at 2 hours post-injury in a sample of 28 adult athletes, and compared to the same symptoms in 28 uninjured, matched control subjects. Statistical or clinical significance was not reported. Recovery graphs illustrate differences, and are summarized in the manuscript in Table 3.

Summary

There are insufficient data (one study[11]) to make assertions about the prevalence of symptoms at specific time points following a PCE. Supplemental Content 11 (Methods of Reporting Symptoms) lists studies included in this review and reasons why symptoms data could not be used in the analysis.

NEUROLOGIC DEFICITS

Data Synthesis

Four publications containing data about neurologic deficits following a PCE met the criteria for this analysis and are included as evidence for this section.[1,15-17] The only neurologic function tested was balance. All samples were adult athletes, and ranged in size from 26 to 150 participants. A total of 266 participants were assessed. In three studies, 116 subjects served as their own controls with pre-injury baseline testing.[1,15,16] In the fourth study, 94 PCE subjects were compared to 56 uninjured controls.[17]

Interpretation of Supplemental Content 12 (Prevalence of Neurologic Deficits). Supplemental Content 12 is a graphical representation of the results of the neurologic tests reported in the four included publications. Time points are listed across the horizontal axis, and individual neurologic tests measured are listed on the vertical axis. *Thus, each cell represents a measurement taken with a particular test at a particular time point.*

For neurologic deficits, the RCI method of analysis was used in two included studies,[1,15] the Standardized Regression-Based Method (SRB) in one,[17] and mixed model ANOVAs in one.[16] For publications that reported individual patient data, the proportion of subjects who showed a clinically significant decrease in performance for a particular test at a particular time is indicated in the cell.

Results

For the publications included in this analysis, measurement times ranged from immediately after the event to 7 days post-injury. A total of 20 measures of function utilizing 11 neurologic tests were performed during that timespan. Ten of the tests were conducted using the NeuroCom Sensory Organization Test (SOT). Results of the SOT are reported by Composite, Somatosensory Ratio, Visual Ratio, and Vestibular Ratio, and also by testing condition (1 through 6). The eleventh test was the Balance Error Scoring System (BESS). While Cavanaugh et al[16] analyzed SOT data, they did not use the SOT manufacturer's software as their metric.

Of the 20 measures of balance, 12 (60%) showed clinically significant differences between PCEs and comparators within one week of injury. For 5 the results are equivocal, and for 3 there was no difference. Thirty-one percent of the sample tested immediately after the event showed clinically significant decrements in function. Prevalence of decrements at 1 day ranged from 23.8% to 36.5%. By day 2, significant decrements persisted in 8 of 14 tests (57%), and the one test taken at day 7 showed no difference.

Summary

Based on the available evidence, the following assertions have been derived:

- Balance deficits within two days: prevalence ranges from 23.8% to 36.5% within 24 hours of injury, and decreases to between 19.2% and 24% by day 2.
- Balance taken at fixed time points between 1 and 7 days: 60% of the measures indicate decrements in function in PCE subjects.

COGNITIVE DEFICITS

Data Synthesis

Nine publications containing data about cognitive deficits following a PCE met the criteria for this analysis and are included as evidence for this section.[1,2,5,8,9,12,14,18,19] (Results from three independent samples were reported in Broglio et al; N=23, 28, and 24.[1] Thus, samples sizes for the study vary in this report.)

One of the nine reported on hospital patients[5]; the other eight took place in athletic environments. Sample sizes ranged from 16 to 122 participants. A total of 604 participants who had sustained a PCE were assessed. There were 720 control participants; 444 served as their own controls in pre-trauma baseline testing, and 276 were from “other injury” or “no injury” comparison groups. Measurement times ranged from immediately after the event to 7 days post-injury. A total of 100 measures of function utilizing 27 cognitive tests were performed during that time span.

Interpretation of Supplemental Content 13 (Prevalence of Cognitive Deficits). Supplemental Content 13 is a graphical representation of the results of the cognitive tests reported in the nine included publications. Time points are listed across the horizontal axis, and individual cognitive tests measured are listed on the vertical axis, grouped according to the cognitive domains of Reaction Time, Attention/Processing Speed/Working Memory, Memory, Executive Function (ability to behave appropriately), Motor/Sensory, and Global Measures. *Thus, each cell represents a measurement taken with a particular test at a particular time point.*

Three methods of indicating a difference between groups for any given test were used:
(1) the proportion of participants with a PCE who had a clinically significant difference from Control measures based on a reliable change index (RCI) (see Supplemental Content 14, Reliable Change Index); (2) a statistically significant difference in mean scores between PCE and Control groups; and (3) visual inspection of recovery curves (eg, recovery curve lines for PCE and Control groups are visually distinct). Visual inspection was used only for publications that did not report RCIs or significance tests.

The highlighted cells in the table indicate results of a particular test (y axis) at a particular time point (x axis). The bright yellow cells indicate evidence supporting clinically or statistically significant differences, or observed differences in recovery curves. Black cells indicate evidence for no differences. The pale yellow cells represent outcomes for which the significance of the result is uncertain. Dark green cells indicate no studies for that SSD at that time point were included in this analysis.

The datum in each cell is the quantitative result for the given outcome at the given time point. There are 4 ways that quantitative data are recorded in Supplemental Content 13:

1. The proportion of the sample with a clinically significant decline in performance from baseline or compared to controls, using an RCI analysis, is recorded in the cell. For example, "71.4% RCI" means that, for the given test at the given time point, there were clinically significant differences between PCE scores and what was expected based on the RCI norms for 71.4% of the sample. The absence of any differences based on the RCI is indicated by "No Diff RCI."

2. "+RCI" indicates the group mean score was below the lower end of the confidence interval for the normed RCI value; "–RCI" indicates the group mean score was inside the confidence interval for the normed RCI value.

3. Presence or absence of statistically significant differences between group means is indicated by "SD" or "No SD" in the cell.

4. When visual inspection of recovery curves was the only available analysis, the appearance or lack of appearance of a difference at a given time point is indicated by "Recovery Curve – Yes" [RC-Yes], or "Recovery Curve – No" [RC-No].

The last number in each cell is the reference for the publication providing the datum for that cell.

Results Across Time

Immediately after the PCE, all tests (5 of 5) showed statistically significant differences between PCE and Control on measures of cognitive function. All 5 measures were from the same study and were five modules from the Standardized Assessment of Concussion (SAC)[19]; Concentration ($p < 0.0001$), Orientation ($p < 0.006$), Immediate Memory ($p < 0.0001$), Delayed Recall ($p < 0.001$), and Total Score ($p < 0.0001$). Of a total sample of 94 players, 45 high school and college football players were measured pre-season and at the time of the concussive event. Loss of consciousness (LOC) occurred in 6.4% of the total sample; post-traumatic amnesia (PTA) in 19.1%.

At 1 day post-injury, 15 of 26 tests showed clinically or statistically significant differences between PCE and Control measures; 6 showed no differences, and for 5, the results are equivocal. Three studies contributed data for this time.[1,2,18] Seventeen cognitive tests were used.

Clinically or statistically significant differences between PCE and Control scores were reported for HeadMinder Simple and Complex Reaction Time, ImPACT Reaction Time, HeadMinder Processing Speed, HVLT Total Score,[2,18] ImPACT Verbal Memory, and the Brief Visual Spatial Memory Test-Revised (BVMT-R) Total and Delayed Scores. Equivocal results were reported for Digit Span, HVLT Total Score,[1] ImPACT Visual Memory, the Controlled Oral Word

Association Test (COWAT),[1] and the ImPACT Motor Processing Speed module. No differences were noted for the COWAT,[2] and the Grooved Pegboard.

Contradictory results were reported on Day 1 between two studies for the Trails A,[1,2] Trails B, and Symbol-Digit tests. Both samples were adult athletes, and both used the AAN parameters for case ascertainment. The Broglio et al[1] sample included football, soccer, basketball, cheering, equestrian, and softball (N = 23 tested with Trails A & B, and Symbol Digit); subjects served as their own controls; 6.7% of the total sample (N = 75) had LOC. The Collins et al[2] sample included only football players (N = 19 at injury, N = 16 for outcomes); 10.5% had LOC. They used a control group of uninjured football players (N = 10). Both studies analyzed outcomes using an RCI. Whereas Broglio et al[1] found 52.2% of the sample had clinically significant declines from baseline in the three tests, Collins et al found no difference between groups. The difference in comparators (self-as-controls vs control group) could account for the different findings, but does not provide information supporting one finding over the other.

Contradictory results were also reported on Day 1 between two studies for the Hopkins Verbal Learning Test (HVLT) Delayed Recall.[2,18] As stated, Collins et al[2] included adult football players (N = 16, 10.5% LOC) and compared them to matched controls (N = 10). Field et al[18] reported results separately for high school (N = 19) and college (N = 35) football and soccer athletes, using subjects as their own controls as well as uninjured, matched controls from the same baseline samples (N = 20 and 18 for high school and college samples, respectively). Overall LOC was 26%; 11% for the high school sample and 34% for the college sample. The RCI analysis from Collins et al.[2] indicated a clinically significant difference in the HVLT Delayed Recall scores of approximately 1 sd below expected at Day 1. The Field et al[18] multivariate and univariate analyses found significant differences between PCE and Controls on the HVLT Delayed Recall for the college sample (mean 7.5 [sd 2.7] PCEs; 9.3 [1.9] Controls; $p < 0.002$), but no difference for the high school sample (7.3 [2.4] PCEs; 8.4 [2.7] Controls). These findings suggest comparability between the two college samples, and call into question pooling results for younger vs older athletes.

<u>At 36 hours post-injury,</u> one study reported results of the Memory Composite of the ImPACT battery (Lovell 2003).[9] Fifty-seven adolescent football, basketball, soccer, and other high impact athletes performed significantly lower on this test at 36 hours post-injury than their own pre-season baseline performance ($p = 0.017$).

<u>At 2 days post-injury,</u> 6 of 15 tests showed clinically or statistically significant differences between PCE and Control measures; 8 showed no differences, and for 1, the results are equivocal. Three studies contributed data for this time.[8,12,14] Eleven cognitive tests were used.

Clinically or statistically significant differences between PCE and Control scores were reported for ImPACT Reaction Time and Verbal Memory. Equivocal results were noted for Symbol Digit. No differences were reported for HVLT Recognition, Delayed Recall, and Immediate Memory, and for Trails B, the COWAT, and Stroop.

Contradictory results were reported on Day 2 between two for the ImPACT Visual Memory and Motor Processing Speed tests.[8,14] Both samples included adult and adolescent athletes from various high-impact sports activities, and compared PCE test scores to subjects' own pre-season baseline test scores. Sample size for Kontos et al[8] was 96, with 1% LOC and 2% PTA. Sample size for Van Kampen et al[14] was 122, with 12.3% LOC and 53.3% retrograde amnesia (RA). Analysis of variance found the Day 2 scores for the Kontos et al[8] sample to be significantly lower than pre-season baseline scores on the ImPACT Visual Memory and Motor Processing Speed tests ($p < 0.05$). No clinically significant difference using an RCI was found for those measures by Van Kampen et al[14] These studies are very similar, and a review of the details of their assessment of potential for bias indicates equivalence in quality. The only difference noted is in the method of analysis, with the RCI suggesting no clinically significant differences, and the ANOVA indicating statistically significant differences.

<u>At 3 days post-injury,</u> 4 of 13 tests showed clinically or statistically significant differences between PCE and Control measures; 9 showed no differences. Two studies contributed data for this time point.[2,18] Nine cognitive tests were used.

Statistically significant differences between PCE and Control scores were reported for the BVMT-R Total and Delayed Scores. No differences were reported for Trails A and B, Symbol Digit, the COWAT, and Grooved Pegboard.

Contradictory results were reported on Day 3 between two studies for the HVLT Total Score and Delayed Recall.[2,18] A comparison of these studies is provided for results reported at Day 1. At the Day 3 time point, the RCI analysis[2] indicated clinically significant differences in the HVLT Total and Delayed Recall, whereas the multivariate and univariate analyses[18] found no significant differences on these tests for either the high school or college samples.

<u>At 4 days post-injury,</u> one study reported results of the Memory Composite of the ImPACT battery.[9] As with the same study for the 36-hour time point, subjects performed significantly lower on this test at 4 days post-injury than their own pre-season baseline performance ($p = 0.004$).

<u>At 5 days post-injury,</u> 1 of 13 tests showed a statistically significant difference between PCE and control measures; 10 showed no differences, and for 2 the results are equivocal. Two studies contributed data for this time point.[2,18] Nine cognitive tests were used.

One statistically significant difference was found on Day 5 for the BVMT-R Total Score ($p < 0.008$). Equivocal results were noted for the HVLT Total Score and Delayed Recall tests. No differences were reported for Trails A and B, Symbol Digit, HVLT Total and Delayed Recall, BVMT-R Delayed, the COWAT, and Grooved Pegboard.

<u>At 7 days post-injury,</u> 2 of 25 tests showed a statistically significant difference between PCE and control measures; 20 showed no differences, and for 3 the results are equivocal. Five studies contributed data for this time point.[2,8,9,12,18] Seventeen cognitive tests were used. Summaries of these studies are provided earlier in this section.

One study reported significantly lower scores at Day 7 than subjects' pre-season baseline scores on the Memory Composite of the ImPACT battery ($p = 0.037$).[9] Equivocal results were noted for

Symbol Digit, HVLT Delayed Recall, and Trails B. No differences were reported for ImPACT Reaction Time, Verbal Memory, Visual Memory, and Motor Processing Speed, and for Trails A and B, Symbol Digit, HVLT Recognition, Delayed Recall, and Immediate Memory, BVMT-R Total Score and Delayed, the COWAT, the Stroop, and Grooved Pegboard.

Contradictory results were reported on Day 7 between two studies for the HVLT Total Score.[2,18] A comparison of these studies is provided for results reported at Day 1. At the Day 7 time point, the RCI analysis[2] indicated no clinically significant differences in the HVLT Total Score, whereas the multivariate and univariate analyses[18] found a significant difference on this test for the high school sample ($p < 0.005$) but not the college sample ($p < 0.70$).

Summary – Results Across Time

Table 4 of the manuscript shows the number of tests conducted at each time point; the proportion of tests that found differences between PCE and controls, or between pre/post PCE measures; and the number of studies contributing data at each time point. Time points were removed for which only one study and a limited number of tests contributed data. Results are displayed in Figure 1 of the manuscript. As can be seen, the proportion of tests showing decrements in function decreases from 58% on Day 1 to 8% on Day 7.

Based on the available evidence, the following assertions have been derived:

- Within **24 hours** of injury, 58% of the cognitive tests in this analysis showed decrements in function for individuals sustaining a PCE.
- Within **48 hours** of injury, 40% of the cognitive tests in this analysis showed decrements in function for individuals sustaining a PCE.
- Within **3 days** of injury, 31% of the cognitive tests in this analysis showed decrements in function for individuals sustaining a PCE.
- Within **5 days** of injury, 8% of the cognitive tests in this analysis showed decrements in function for individuals sustaining a PCE.
- Within **7 days** of injury, 8% of the cognitive tests in this analysis showed decrements in function for individuals sustaining a PCE.
- One study suggests that decrements in function may be present in significantly more subjects immediately after injury than at Day 1 and beyond.
- Two studies with contradictory findings suggest that type of control group (self vs controls) could account for differences in outcome.
- Two studies with contradictory findings suggest that in athletic populations, age (eg, high school vs college) could account for differences in outcome.
- Four studies with contradictory findings suggest that type of analysis could account for differences in outcome.

Results Across Cognitive Tests

Reaction Time Three publications used measures of reaction time to test a total of 270 individuals suspected of sustaining a concussion.[1,8,14] One study included 2 independent samples.[1] Two included adults and adolescents (N = 96 & 122, respectively),[8,14] and one included adults (N = 52).[1] All used the Reaction Time module from ImPACT. One also used the Simple and Complex Reaction Time tests from HeadMinder.[1] All were athletic populations and used individuals as their own comparators in pre-season baseline assessments.

A total of six assessments occurred across days 1, 2, and 7 post-injury. Of the three tests taken on day 1, 71.4% of participants had clinically significant declines in performance from baseline on the HeadMinder Simple and Complex Reaction Time tests, and 41.7% had clinically significant declines on the ImPACT Reaction Time module. Of the two tests on day 2, one showed a statistically significant decline from baseline ($p < 0.05$), and for the other, the difference between baseline and post-injury group means fell below the established RCI value. No difference from baseline was found in the one test taken at day 7. Thus five of six assessments of reaction time (83%) showed decrements in performance for PCE subjects in the first week after injury.

<u>Attention/Processing Speed/Working Memory</u> Four publications used measures of attention/processing speed/working memory to test for cognitive deficits; three in adult athletes,[1,2,12] and one in adults and adolescents.[19] Instruments included HeadMinder Processing Speed, Trails A, Symbol Digit, Digit Span, and the Concentration module of the Standardized Assessment of Concussion (SAC). Three of the studies used individuals as their own controls (N = 51, 16, & 45 respectively)[1,2,19]; the fourth compared athletes diagnosed with concussion (N = 94) to uninjured athletes (N = 56).[12] A total of 262 participants were tested; 15 assessments occurred from immediately following injury through days 1, 2, 3, 5, and 7.

The SAC Concentration module was used to assess subjects immediately after injury and showed a statistically significant difference in mean scores when compared to the same subjects' pre-injury baseline scores ($p < 0.0001$).[19]

One study using an RCI found that when measured within 24 hours of injury, 50% of PCE subjects (N = 28) had clinically significant decrements in performance on the HeadMinder Processing Speed test, and 30.4% had clinically significant decrements in performance on the Digit Span test when compared to their own baseline scores (N = 23).[1]

As discussed in the previous section, two studies found contradictory results on the Trails A and Symbol Digit tests at day 1.[1,2] Broglio et al[1] found that 52.2% of participants had clinically significant decrements in performance on these tests when compared to their own pre-injury baseline scores, whereas Collins et al[2] found no difference using an RCI analysis at days 1, 3, 5, and 7. The key difference between the studies was that Broglio et al[1] compared post-injury to pre-injury scores in the same participants, and Collins et al[2] used a comparison group.

One study compared performance on the Symbol Digit Test between a PCE Group (N = 94) and control group (N = 56) at days 2 and 7.[12] While statistical or clinical significance were not reported, visual inspection of the recovery curves suggest group differences.

In fifteen measures of attention/processing speed/working memory, seven (47%) showed decrements in performance for PCE subjects in the first week after injury.

Memory Eight publications used measures of memory to test for cognitive.[1,2,8,9,12,14,18,19] Instruments included the Hopkins Verbal Learning Test (HVLT) Total Score, Recognition, Delayed Recall, and Immediate Memory; the ImPACT Verbal Memory, Visual Memory, and Memory Composite; the Standardized Assessment of Concussion (SAC) Orientation, Immediate Memory, and Delayed Recall; and the Brief Visual Spatial Memory Test-Revised (BVMT-R) Total Score and Delayed Recall.

All studies took place in athletic environments. Specific details are provided earlier, and in an Evidence Table (Supplemental Content 6). A total of 625 participants were tested; fifty-three assessments occurred from immediately following injury through days 1, 2, 3, 5, and 7.

Global Memory Measures Of five global measures of memory taken on day 1 (4 of HVLT Total and 1 of BVMT-R Total), four showed statistically or clinically significant differences in performance between PCE and comparators; for one the results are equivocal. Of four taken on day 3, two showed differences, and two did not. Of four taken on day 5, one showed differences, two did not, and for one the results are equivocal. Of four taken on day 7, one showed differences, and three did not. Additionally, one memory composite test (ImPACT) taken at 36 hours and 4 days post-injury showed statistically significant decrements in performance for PCE subjects.

Immediate Memory One measure of immediate memory taken immediately after impact showed a statistically significant difference between scores compared to pre-trauma baseline scores in the same subjects. Two taken at day two, and two at day 7 showed no differences.

Delayed Recall One measure of delayed recall taken immediately after injury showed a statistically significant difference compared to pre-trauma baseline scores in the same subjects. Of four measures taken at day 1, three showed statistically or clinically significant differences, and one did not. One measure taken at day 2 showed no difference. Of four measures taken at day 3, two showed differences and two did not. Of four measures taken at day 5, 3 showed no differences, and for 1 the results are equivocal. Of five measures taken at day 7, 4 showed no differences, and for 1 the results are equivocal.

Verbal Memory Verbal memory was measured using the ImPACT module once on day 1, twice on day 2, and once on day 7. The day 1 and 2 measures showed statistically or clinically significant differences between groups; by day 7 there was no longer a difference.

Visual Memory Similarly, visual memory was measured using the ImPACT module once on day 1, twice on day 2, and once on day 7. The results for day 1 are equivocal. On day 2, one study showed a statistically significant difference, and the other showed no difference using an RCI analysis. The day 7 measure showed no difference.

Orientation Orientation was measured once immediately after the injury, and showed a statistically significant difference between scores compared to pre-trauma baseline scores in the same subjects.

In sum, in fifty-three measures of memory, twenty-three (43%) showed decrements in performance for PCE subjects in the first week of injury.

Executive Function Three publications used measures of executive function to test for cognitive deficits.[1,2,12] Instruments included Trails B, the Controlled Oral Word Association Test (COWAT), and the Stroop. All studies took place in athletic environments. Specific details are provided earlier, and in an Evidence Table (Supplemental Content 6). A total of 189 subjects were tested; sixteen assessments occurred on days 1, 2, 3, 5, and 7.

The only clearly significant finding was with Trails B on day 1; Broglio et al[1] found that 52.2% of subjects who had sustained a PCE had clinically significant declines in performance on this test when compared to their own pre-injury baseline measures. However, Collins et al.[2] also using an RCI analysis, found no difference on day 1 for Trails B. Results of one measure taken at day 7 are equivocal. The remaining measures show no differences.

Of seven measures using the COWAT, six showed no differences between PCE and controls, and for one, taken at day 1, the results are equivocal. The Stroop was used on days 2 and 7 in one study, showing no differences at either time point.

In sixteen measures of executive function, one (6%) showed decrements in performance for PCE subjects in the first week of injury.

Motor/Sensory Four publications used motor/sensory measures to test for cognitive deficits.[1,2,8,14] Instruments included were the ImPACT Motor module and the Grooved Pegboard. All studies took place in athletic environments. Specific details are provided earlier, and in an Evidence Table (Supplemental Content 6). A total of 258 subjects were tested; eight assessments occurred on days 1, 2, 3, 5, and 7.

Kontos et al found subjects performed significantly worse at day 2 on the ImPACT Motor module when compared to their own pre-trauma baseline scores. However, using an RCI analysis, Van Kampen et al[14] found no clinically significant difference using this test at day 2 when compared to subjects' own pre-trauma baseline scores. For one measure of this module taken at day 1 the results are equivocal. All other measures using either the ImPACT module or the Grooved Pegboard showed no differences.

In eight measures of motor/sensory function, one (12.5%) showed decrements in performance for PCE subjects in the first week of injury.

Global Measures of Function One publication used a global measure of function to test for cognitive deficits.[19] The instrument was the Standardized Assessment of Concussion (SAC) Total Score. McCrea et al[19] compared scores from immediately after injury to pre-trauma baseline scores in 45 athletes, and found a statistically significant decline.

Summary – Results Across Cognitive Tests

Table 5 of the manuscript shows the number of tests conducted for each cognitive domain; the proportion of tests that found differences between PCE and comparators; and the number of studies contributing data at each time point. The domain was removed for which only one study and one test contributed data. Results are displayed in Figure 2 of the manuscript.

Based on the available evidence, the following assertions have been derived:

- **Reaction Time.** Prevalence of deficits ranges from 41.7% to 71.4% within 24 hours in injury, and persist through 2 days post-injury to a significant degree, although the exact prevalence is not known beyond 1 day.
- 83% of the measures of **reaction time** taken between 1 and 7 days post-injury indicate decrements in function for this domain in PCE subjects compared to controls.
- **Attention/Processing Speed/Working Memory.** Prevalence of deficits ranges from 0 to 30.4%, to 50%, and to 52.2% within 24 hours of injury, with no evidence that they persist beyond this time point.
- 29% of the measures of **attention/processing speed/working memory** taken between 1 and 7 days post-injury indicate decrements in function for this domain in PCE subjects compared to controls.
- **Memory.** Prevalence of deficits ranges from 0 to 20.8%, to 39.1%, to 41.7% within 24 hours of injury, and persist to a significant degree in 2 of 14 tests by day 7, although the exact prevalence is not known beyond day 1.
- 43% of the measures of **memory** taken between 1 and 7 days post-injury indicate decrements in function for this domain in PCE subjects compared to controls.
- **Executive Function.** Prevalence of deficits ranges from 0 to 34.8%, to 52.2% within 24 hours of injury, with no evidence that they persist beyond this time point.
- Prevalence data are not available for deficits identified with measures of **motor/sensory function.**
- Prevalence data are not available for deficits identified with **global cognitive measures.**

Key Question 2 Does the presence of signs, symptoms, and deficits within three months of a potential concussive event vary by demographics, pre-morbid conditions, co-morbidities, mechanism of injury, case definition, or other factors independent of the potential concussive event?

Data Synthesis

Four publications met the criteria and are included as evidence for this question (see Evidence Table, Supplemental Content 6).[2,4,7,8] All took place in athletic environments; two with adults and two combining adults and adolescents. Two studies compared differences on outcome measures between players with and without previous concussions.[2,7] Collins et al[2] also assessed the influence of learning disability (LD) on outcome. One study[4] assessed sex differences, and one[8] differences on outcomes between Caucasian and African American subjects.

Results

Previous Concussions

Collins et al[2] compared measures of neuropsychologic function in 386 male college football players, in which 179 had no history of previous concussion, 129 had sustained 1 previous concussion, and 78 had sustained two or more previous concussions. Tests included the HVLT Total Score and Delayed Recall, Trails A and B, Digit Span, Symbol Digit, Grooved Pegboard Dominant and Non-Dominant Hand, and the COWAT. Although tests were taken at pre-season baseline, and at 1, 3, 5, and 7 days post-injury for subjects in the cohort that sustained an in-season concussion, the differences based on previous concussion were only reported for baseline measures for the entire cohort. Subjects in the group with $\geq$ 2 previous concussions performed significantly worse on Trails B and Symbol Digit than those with no previous concussions ($p = 0.02$ and 0.008, respectively); and also significantly worse than those with one previous concussion ($p < 0.001$ for both). Authors report that SAT and ACT scores for the group with $\geq$ 2 previous concussions were higher than for the other two groups, indicating the difference in scores of neuropsychological tests could not be attributed to baseline differences in aptitude.

Iverson et al (2004) compared the ImPACT measures of Reaction Time, Processing Speed, and the Memory Index between subjects with 3 or more previous concussions and those without a history of previous concussion (N = 19 in each group).[7] The sample included various high impact athletic activities, and both adolescent and adult subjects. Measures were taken at pre-season baseline, and between 1 and 5 days post-injury. Unlike the Collins et al[2] study, only results for participants who sustained an in-season concussion were reported. No group differences were found for the Reaction Time and Processing Speed tests. For the Memory Index, a significantly greater proportion of the group with $\geq$ 3 previous concussions sustained a major reduction in performance from baseline to post-injury (47.4%) than the group without prior concussions (10.5%) (chi-squared [1, 38] = 6.3, $p < 0.013$). The odds of a significant drop in memory function was 7.7 times greater for the group with concussion history than the group without (95% CI = 1.4 – 42.7). Major reduction was defined as a 14-point drop in the Memory Index score.

To summarize, in a large sample of adult athletes, for two of nine tests of cognitive function (22%), pre-injury scores were significantly worse for athletes who had sustained $\geq$ 2 concussions than for those without a previous concussion history.[2] A second study of a small sample of adolescent and adult athletes suggests the odds of sustaining a 14-point drop in the ImPACT Memory Index within 5 days of injury are 7 to 8 times greater for athletes who sustained prior concussions than those with no history of concussion; a difference was found in one of three (33%) tests for this study.[7]

Learning Disability (LD)

In a sample of 386 male college football players, athletes with (N = 54) and without (N = 332) a diagnosis of LD were compared for baseline scores on the HVLT Total Score and Delayed Recall, Trails A and B, Digit Span, Symbol Digit, Grooved Pegboard Dominant and Non-Dominant Hand, and the COWAT.[2] There were no significant differences.

Sex

Covassin et al[4] compared the four ImPACT measures of Verbal Memory, Visual Memory, Reaction Time, and Processing Speed at pre-injury baseline, 1 – 3 days post-injury, and 7 – 10 days post-injury between 41 male and 38 female athletes who had sustained a PCE. In one of the four tests (25%), Visual Memory, females performed significantly worse than males at the 1 – 3 day post-injury interval ($F[1, 77] = 11.26$; $p = 0.001$). In a comparison of signs and symptoms, males reported significantly more vomiting ($F[1, 77] = 5.95$; $p = 0.017$) and sadness ($F[1, 77] = 13.05$; $p = 0.001$) than females. However, a complete list of signs and symptoms that were measured was not provided.

Race

Kontos et al[8] compared the four ImPACT measures at pre-injury baseline and at 2 and 7 days post-injury between 48 African American and 48 Caucasian adolescent and adult athletes from various high-impact sports activities. While Caucasians performed significantly better than African Americans on the Processing Speed module, authors attribute the difference to an increase from baseline for Caucasians due to a practice effect. Based on a Reliable Change Estimate (RCE) analysis and odds ratios, at 7 days post-injury African American athletes were 2.4 times more likely to have a clinically significant decline than Caucasian athletes (chi-squared = 4.29; $p = 0.03$).

Key Question 3 What is the association between different signs, symptoms, and, or between the same signs, symptoms, or deficits at different time points for the same patients, following a potential concussive event?

Data Synthesis

Four publications met the criteria and are included as evidence for this (see Evidence Table, Supplemental Content 6).[5,9,15,19] Three took place in athletic environments; one with adults, one with adolescents, and one combining adults and adolescents. A fourth study assessed adult and pediatric hospital patients.[5] Three studies examined the relationship between severity estimates and measures of function on cognitive tests.[5,9,19] One examined the association between symptoms and cognitive function.[15]

Results

Signs and Cognitive Function

Lovell et al[9] (2003) divided a sample of 57 adolescent athletes who had sustained a PCE into More Severe (N = 13) and Less Severe (N = 43) groups based on duration of amnesia or disorientation (> 5 min. or < 5 min., respectively). Athletes were assessed with the ImPACT Memory Composite at pre-injury baseline, and at 36 hours, 4, and 7 days post-injury. An analysis of variance indicated that average scores on the composite were significantly lower for the More Severe than the Less Severe group ($F[1, 54] = 5.5$; $p < 0.024$). Pairwise comparisons showed significant declines from baseline in composite scores for the More Severe group persisted to day 7 ($p < 0.037$), whereas the Less Severe group persisted to day 4 ($p < 0.013$), with no difference from baseline and day 7.

McCrea et al (2002) created three severity groups – No LOC/No PTA (N = 76), PTA/No LOC (N = 8), and LOC+PTA (N = 7) and conducted post-hoc comparisons with Bonferroni correction on their SAC scores measured immediately after injury.[19] Average SAC scores for the LOC+PTA group were significantly lower than the No LOC/No PTA group (mean difference 11.86; $p < 0.0001$) and the PTA/No LOC group (mean difference 8.36; $p < 0.0001$). Average SAC scores for the PTA/No LOC group were significantly lower than the No LOC/No PTA group (mean difference 3.50; $p = 0.007$).

In the one study conducted in a hospital sample, 90 patients diagnosed with mild TBI were divided into groups of PTA (N = 42) and No PTA (N = 48), and compared on a set of neuropsychological tests within 24 hours of injury.[5] Because the tests were adapted and there was no report of them being validated, only the Digit Symbol test could be used for this analysis. The PTA group had significantly lower scores on the Digit Symbol test within 24 hours post-injury than the No PTA group ($t_{88} = 6.25$; $p < 0.001$).

Symptoms and Cognitive Function

Broglio et al[15] published results of an analysis of the relationship between self-report of cognitive symptoms and objective measures of cognition (N = 32), and of self-report of neurologic symptoms and objective measures of balance (N = 26) among university athletes. ImPACT was used to assess cognitive function, and the NeuroCom Sensory Organization Test (SOT) was used to assess balance. Subjects served as their own controls with pre-injury baseline testing, and post-injury measures were performed within 48 hours of injury. There were significant correlations between the symptoms “Feeling Mentally Foggy” and the ImPACT Reaction Time score ($p = 0.03$); “Difficulty Concentrating” and Verbal Memory ($p = 0.01$); and “Difficulty Remembering” and Verbal Memory ($p < 0.001$) and Reaction Time ($p = 0.03$). For balance, there were significant correlations between the symptoms “Balance Problems” and the SOT Composite ($p < 0.001$), Somatosensory Ratio ($p = 0.03$), Visual Ratio ($p = 0.04$), and Vestibular Ratio ($p < 0.001$); and between the symptom “Dizziness” and the SOT Composite ($p < 0.001$) and Vestibular Ratio ($p = 0.01$).

Key Question 4 What is the relationship between signs, symptoms, and deficits, and injury imaging or biomarkers of injury following a potential concussive event?

Data Synthesis

Seven publications met the criteria and are included as evidence for this question (see Evidence Table, Supplemental Content 7).[20-26] Four reported on the relationship between CT scans and

SSDs,[23-26] and three[20-22] on biomarkers and SSDs. All took place in hospital environments; four with adult samples, two with adult and pediatric patients, and one with pediatric patients only.

Results – CT Scan

Signs and CT Scan Findings

Supplemental Content 15 summarizes the publications included in this analysis that considered the utility of CT scan technology in assessing patients with PCE. A total of 4,803 patients were scanned within 24 hours of injury. Of those, 360 patients had positive findings on CT scan (7.5%); prevalence of positive findings across studies ranged from 4.7% to 19%. For signs, two studies associated CT with LOC, one with LOC/Amnesia, three with GCS 13, four with GCS 14, three with amnesia, one with nausea/vomiting, one with nausea, three with vomiting, and two with seizures. For symptoms, three studies associated CT with headaches, one with dizziness, one with blurred vision, and one with abnormal behavior. For neurologic deficits, one study associated CT with presence of focal neurologic deficits, one with pupil abnormalities, and one with nystagmus. No study meeting inclusion criteria considered the association between CT and measures of cognitive function.

GCS 13 Evidence from one study indicates the probability of having a positive finding on a CT scan is four times greater for subjects with GCS 13 than for those with GCS 15.[24] A second study reported a significant correlation between GCS and positive findings on CT scan.[23]

PTA Evidence from one study indicates the probability of having a positive finding on a CT scan is over 7 times greater for subjects who had PTA $\geq$ 4 hours post-injury than for those with shorter or no PTA.[24] A second study reported a significant correlation between retrograde amnesia and positive CT scan findings.[23] A third study showed a four-fold increase in the probability of having a positive finding on a CT scan with for subjects with LOC/PTA.

Vomiting Evidence from two studies indicates the probability of having a positive finding on a CT scan ranges from approximately 2.5 to 4.5 times greater for subjects who experienced vomiting than for those who did not.[24,25] A third study reported a significant correlation between vomiting and positive CT scan findings.[23] A fourth study that used the category “nausea/vomiting” (implying “either/or”) reported the probability of having a positive finding on a CT scan was 4.5 times greater for subjects who experienced nausea/vomiting than for those who did not.[26]

Symptoms, Neurologic Deficits, Cognitive Deficits, and CT Scan Findings

The data about the association between CT and symptoms and neurologic deficits are contradictory or equivocal (see Table, Supplemental Content 15). No study meeting inclusion criteria considered the association between CT and measures of cognitive function.

Results - Biomarkers

One study measured S100B and neuron-specific enolase (NSE) within 6 hours of injury in a hospital sample of pediatric patients; 95 with diagnosed mild TBI, and 53 diagnosed with contusion.[20] Patients with focal neurological signs were excluded. No significant difference was found in levels of S100B or NSE between patients with GCS 14 and those with GCS 15.

One study measured Ubiquitin C-terminal Hydrolase (UCH-L1) within 4 hours of injury in a sample of 86 patients diagnosed with mild TBI, and compared to UCH-L1 in uninjured controls (N = 176) and trauma controls (N = 23).[22] There were significantly greater levels of UCH-L1 in patients with GCS 13-14 than trauma controls ($p = 0.006$).

A second study by Papa et al[21] measured Glial Fibrillary Acidic Protein Breakdown Products (GFAP-BDP) within 4 hours of injury in a sample of 97 patients diagnosed with mild TBI, and compared to GFAP-BDP in uninjured controls (N = 176) and trauma controls (N = 23).[21] There were significantly greater levels of GFAP-BDP in patients with GCS 13-14 than trauma controls ($p = 0.011$).

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