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Clinical commentary

Anterograde amnesia and disorientation are associated with in-patients *without* traumatic brain injury taking opioids. Retrograde amnesia (RA) is absent. RA assessment should be integral to post-traumatic amnesia testing

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ABSTRACT

The Glasgow Coma Scale (GCS) only assesses orientation after traumatic brain injury (TBI). 'Post-traumatic amnesia' (PTA) comprises orientation, anterograde amnesia (AA) and retrograde amnesia (RA). However, RA is often disregarded in formalized PTA assessment. Drugs can potentially confound PTA assessment: e.g. midazolam can cause AA. However, potential drug confounders are also often disregarded in formalized PTA testing. One study of medium-stay elective-surgery orthopaedic patients (without TBI) demonstrated AA in 80% taking opiates after general anesthesia. However, RA was not assessed. Opiates/opioids are frequently administered after TBI. We compared AA and RA in short-stay orthopaedic surgery in-patients (without TBI) taking post-operative opioids after opiate/opioid/benzodiazepine-free spinal anesthesia. In a prospective cohort, the Westmead PTA Scale (WPTAS) was used to assess AA (WPTAS < 12), whilst RA was assessed using the Galveston Orientation and Amnesia Test RA item. Results were obtained in n = 25 (60 ± 14 yrs, M:F 17:8). Surgery was uncomplicated: all were discharged by Day-4. All were taking regular oxycodone as a new post-operative prescription. Only one co-administered non-opioid was potentially confounding (temezepam, n = 4). Of 25, 14 (56%) demonstrated AA: five (20%) were simultaneously disorientated. Mean WPTAS was 11.08 ± 1.22. RA occurred in 0%. *Conclusions*: AA and disorientation, but not RA, were associated with in-patients (without TBI) taking opioids. Caution should therefore be applied in assessing AA/orientation in TBI in-patients taking opioids. By contrast, retrograde memory was robust and more reliable: even in older patients with iatrogenic AA and disorientation. RA assessment should therefore be integral to assessing TBI severity in all formalized PTA and GCS testing.

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1. Introduction

The Glasgow Coma Scale (GCS) is widely used to determine conscious level after traumatic brain injury (TBI) [1]. However, the GCS only assesses orientation [1]. The post-TBI syndrome, incompletely referred to as 'post-traumatic amnesia' (PTA) [2], comprises disorientation as well as retrograde amnesia (RA: defective memory of events prior to TBI) and anterograde amnesia (AA: defective memory subsequent to TBI). Noting that orientation usually recovered first [2], Russel and Symonds, two of the earliest pioneers in post-TBI assessment, emphasized the equal importance of both RA and AA testing in determining TBI recovery [2–9]. In particular, Russel opined that if, after TBI "..a patient is able to correctly describe events preceding the loss of consciousness by only a few minutes or seconds, then consciousness has returned in full" [3]. However, despite such emphasis, most current formalized PTA testing (i.e. in institutions using tests other than the Galveston Orientation and Amnesia Test [GOAT]) omits any RA assessment [2]. Instead, only resolution of orientation and AA is commonly used to determine recovery after TBI, to determine TBI severity, and to determine hospital discharge [2]. Thus, both the GCS and much formalized PTA testing are, potentially, incomplete.

A recent review article also emphasized that the potential effect of concurrent medication, as a potentially confounding factor in

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PTA assessment, is also often disregarded in much formalized PTA assessment after TBI [2]. This is despite the fact that Symonds, in 1942, had specifically cautioned that, for example, "..it is important to know whether the patient has been given morphia" when assessing PTA [8]. Indeed, it is now known that certain drugs (e.g. midazolam) can specifically elicit AA in patients *without* TBI [10]. This fact is exploited in day case procedures, such as endoscopy [10]. Opiates/opioids are frequently administered to TBI patients: either for headache, or for other concurrent injuries. Pertinently, a recent pilot study suggested that as many as 80% of medium-stay elective orthopaedic in-patients (*without* TBI) failed formalized PTA testing criteria whilst receiving opiates after general anesthesia (GA) [11]. However, in common with much formalized PTA practice, RA was not assessed in that study [11]. Thus, while AA may be overestimated, the potential effect of either opiates, or opioids, on RA currently remains unknown.

In Australia, the Westmead PTA scale (WPTAS) is widely used to formally assess PTA after TBI. However, the WPTAS does not include a history of drug use, and it does not formally assess RA. We therefore aimed to compare AA and RA in short-stay orthopaedic surgery in-patients (without TBI) taking post-operative opioids after uncomplicated opiate/opioid-free and benzodiazepine-free spinal anesthesia.

2. Methods

A convenience sample of in-patients on an orthopaedic ward in a major regional public hospital were prospectively studied after local ethics committee approval. All patients had undergone elective or semi-elective (typically joint replacement) surgery as a short stay (i.e. less than 4 days) procedure using opiate/opioid-free and benzodiazepine-free spinal anesthesia (bupivacaine combined with propofol sedation) of duration less than 3 h. Patients were included if they were older than 18 yrs and of ASA grade 1 or 2. Patients were excluded if they were regularly taking opioids other than codeine phosphate 15 mg as required, or any other recently prescribed potentially psycho-active drug including tramadol, anti-convulsants, major or minor tranquillizers, amitriptylline, or illicit or prescribed cannabinoids. Patients were also excluded if they had a history of current psychiatric disorder, substance abuse, alcohol abuse, recent or concurrent TBI, or any neurological disorder affecting cognition, memory or conscious level. Finally, patients were excluded if spinal anesthesia duration was greater than 3 h, or if surgery had been in any way complicated. All participants were given an information sheet detailing the study before signing a consent form in agreement to participate.

The WPTAS was used to assess AA [12]. WPTAS < 12 was considered to indicate evidence of AA [12]. Since there is no evidence for three consecutive WPTAS day testing, and only evidence against it [2,13,14], WPTAS was recorded from only one day of testing. RA was assessed using the GOAT RA item [15]. RA was considered absent if patients could remember key events, in detail, immediately prior to the delivery of spinal anesthesia. All post-operative psychometric testing (WPTAS and GOAT-RA) was performed between 24-36 h after surgery (dependent upon the extent of surgery) in order to minimize any potentially confounding effects of drugs co-administered during surgery [16]. All patients were prescribed oral oxycodone on a regular basis immediately post-operatively as a new prescription in addition to non-steroidal anti-inflammatory agents and paracetomol.

3. Statistical analysis

Normality of score distribution for dependent variables was examined using skewness, kurtosis, stem and leaf plots, and the Shapiro-Wilks statistic. Assumptions of normality were confirmed for all dependent variables. Homogeneity of variance was considered using the Levene Test for Equality of Variance and were not violated. Analysis of variance (ANOVA) was therefore performed with statistical significance determined as $P < 0.05$. Effect sizes (eta squared, η^2) were calculated. According to Cohen (1988) a small η^2 effect size is 0.01, a medium η^2 is 0.06, and a large η^2 0.014 [17].

4. Results

Results were obtained in n = 25 (mean age 60 ± 14 yrs, M:F 17:8) (Table 1). Six (24%) had suffered recent trauma to the region operated: none of these cases, however, had been associated with alcohol. No case had suffered multiple trauma. Sixteen (64%) patients were discharged by Day 2 of surgery, 24 (96%) by Day3 and 100% by Day 4.

All 25 patients (100%) studied were taking the opioid oral oxycodone on a regular basis post-operatively as a standard new prescription. The same treatment is standard for TBI in-patients on the neurosurgery ward. The most commonly co-administered drug was oral oxycodone/naloxone (10/25, 40%) (Table 1): six of these (40%) returned a WPTAS < 12/12. Temezepam was co-administered in four (WPTAS < 12/12 in all four cases). Subcutaneous fentanyl was co-administered in two (WPTAS = 12/12 in both). Buprenorphine was co-administered in one (with WPTAS < 12), whilst codeine (the only opiate) was co-administered in one other (WPTAS = 12/12). Two patients were taking non-tricyclic anti-depressants (Table 1). The opiate morphine was not administered in our study.

The mean WPTAS total score was 11.08 ± 1.22. Those with an abnormal WPTAS were older than those with a normal WPTAS (65.8 ± 10.8 yrs v 55.6 ± 15.5 yrs): however, this was not statistically significant ($P = 0.06$, $\eta^2 = 0.141439$). The mean WPTAS of patients with an abnormal score (WPTAS = 10.3 ± 1.1) was significantly reduced compared to those with a normal score (WPTAS = 12), ($P < 0.0001$, $\eta^2 = 0.517816$). Of 25 patients *without* TBI, 14 (56%) demonstrated evidence of AA (Table 1). Whilst all 56% patients specifically failed memory testing, 5/14 (36%) of these also failed orientation testing: i.e. 5 (20%) were also disorientated. By contrast, 0/25 (0%) demonstrated evidence of RA.

5. Discussion

Certain drugs (e.g. midazolam) can specifically elicit AA in patients *without* TBI [10]. A recent pilot study by Mc Carter et al. also suggested that, of medium-stay elective orthopaedic in-patients without TBI, as many as 80% failed WPTAS testing criteria whilst receiving opiates (i.e. morphine or codeine) [11]. Unfortunately, in keeping with much formalized PTA practice, RA was not assessed [11]. Furthermore, the latter study [11] comprised only 17 patients where some had been hospitalized for longer than in current elective orthopaedic practice [18], and where all had undergone GA [11]. It is therefore possible that some might have suffered confounders related either to a prolonged GA (with potentially significant 'hang-over') or to peri-operative complications. By contrast, all but one in our study had been discharged by Day 3; whilst all had been discharged by Day 4. All had therefore undergone uncomplicated elective or semi-elective surgery using opiate/opioid-free and benzodiazepine-free spinal anesthesia for less than 3 h. Psychometric testing was performed 24–36 h after commencement of regular post-operative analgesia [16].

In contrast to the study of McCarter et al. (where no single opiate was common to all), all our patients were regularly taking the opioid oxycodone as a standard new post-operative prescription.

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