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Analgesia after intracranial surgery: a double-blind, prospective comparison of codeine and tramadol

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We have compared codeine and tramadol in a prospective, double-blind study of postoperative analgesia in 75 patients after elective intracranial surgery. Twenty-five patients received codeine 60 mg, tramadol 50 mg or tramadol 75 mg i.m. Patients receiving codeine had significantly lower pain scores over the first 48 h after operation ($P<0.0001$). Although there was no difference in visual analogue scale (VAS) scores between the three groups at 24 h, the codeine group had significantly lower scores at 48 h ($P<0.0001$). The tramadol 75 mg group had significantly higher scores for both sedation and nausea and vomiting ($P<0.0001$ for both scores). We conclude that codeine 60 mg i.m. provided better postoperative analgesia than tramadol after craniotomy and that tramadol 75 mg should be avoided because of its side effects of increased sedation and nausea and vomiting.

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Codeine phosphate is traditionally the agent most frequently used for pain relief after craniotomy, which is thought to require mild analgesia because of the involvement of skin and dura only. Codeine, with approximately only one-twelfth the potency of morphine,[1] is thought to be a suitable agent and it has been compared with morphine after craniotomy.[2] Despite having several advantages, morphine is used rarely for fears of excessive sedation, meiosis and respiratory depression,[3 4] and therefore the use of codeine continues.

However, codeine phosphate has several disadvantages. It must be given by the oral or i.m. route as i.v. injection may be followed by cardiovascular collapse.[5] It is metabolized by O-demethylation to morphine, which is believed to be its mode of action, but the variable rate of morphine production means its effect is variable in magnitude.[6]

Tramadol is an analgesic introduced relatively recently into the UK,[7] although it has been used in Europe for 20 yr. It may be given orally, i.m. and i.v. in the same dose and it is not a controlled drug. The analgesic effects of tramadol are mediated by at least three mechanisms: it is a weak mu opioid receptor agonist; it inhibits the reuptake of the neurotransmitters 5-hydroxytryptamine (5-HT) and norepinephrine in the descending inhibitory pain pathways[8]; and it facilitates 5-HT release.[9]

Much work has been carried out to assess the potency and side effects of tramadol. It has been demonstrated to be approximately equipotent with pethidine[10] and is not associated with clinically significant respiratory depression.[10 11] This, in addition to lack of sedation[12] or meiosis, make it potentially useful in neurosurgical analgesia, although it has not been studied in this field. It shares with codeine the ability to cause nausea and vomiting.[10] There is also a rarely encountered but potentially serious risk of epileptic fits but these have been reported only after large, rapidly administered i.v. bolus doses.[13]

The aim of this study was to compare postoperative pain relief with codeine and two doses of tramadol, given i.m. after cranial surgery. This was achieved by assessing pain scores, visual analogue scale scores, number of analgesic injections required and use of additional 'escape' analgesia. Side effects of the analgesics, in particular sedation, respiratory and cardiovascular depression, and nausea and vomiting, were also assessed.

Patients and methods

After obtaining approval from the Ethics Committee and informed consent, we studied 75 patients undergoing elective intracranial surgery. Only patients with a Glasgow coma score (GCS) of 15/15 and who were anticipated to be fully conscious after surgery were included. Age limits of 18–75 yr were set and exclusion criteria included body weight less than 50 kg or more than 100 kg. Each patient

Table 1 Postoperative scoring systems[20]

Pain score	Sedation score	Nausea and vomiting score
0 No pain at rest or on movement	1 Awake and co-operative	0 No nausea or vomiting
1 No pain at rest but slight with coughing or movement	2 Agitated/anxious/restless	1 Nausea but no vomiting
	3 Intermittently awake	2 Retching but no vomiting
2 Intermittent pain at rest or moderate pain on coughing or movement	4 Roused by voice	3 Vomiting
	5 Roused by pain	
3 Continuous pain at rest or severe pain on coughing or movement	6 Unrousable	

was instructed on the use of a standard 100-mm visual analogue scale (VAS) before operation to enable assessment of pain in the postoperative period.

A standard anaesthetic technique was used, consisting of premedication with temazepam 20 mg orally, 1 h before surgery, followed by induction of anaesthesia with i.v. infusions of propofol (target-controlled infusion to a plasma concentration of 3–6 $\mu g\ ml^{-1}$) and alfentanil 0.5–1.0 $\mu g\ kg^{-1}\ min^{-1}$, maintained throughout surgery and titrated to clinical response. After administration of atracurium 0.5 mg kg^{-1} and tracheal intubation, the lungs were ventilated with 30% oxygen in air without an inhalation agent and infusion of atracurium was used to maintain neuromuscular block. An arterial cannula and central venous pressure line were inserted in each case, as is our routine practice.

After operation, patients remained in the recovery area for at least 1 h and were not discharged to the ward unless their pain score was 0 or 1. The scoring system used is shown in Table 1

Patients were numbered sequentially and allocated randomly using the closed envelope technique to receive codeine phosphate 60 mg (group 1), tramadol 50 mg (group 2) or tramadol 75 mg (group 3) i.m. after surgery. Two doses of tramadol were studied because of the wide dose range recommended in the literature.[14] The drugs were prepared on a named patient basis in identical volumes by the pharmacy and the identity of the drug was unknown to both the nursing and medical staff managing the patients after operation.

A prepared syringe of the study drug was available in the controlled drug cupboard of the recovery area for each named patient should they require pain relief before discharge to the ward. Analgesia was offered to patients if their pain score was 2 or more and an antiemetic if nausea and vomiting score was 1 or more, although patients could refuse treatment.

In addition to standard postoperative neurosurgical monitoring of heart rate, arterial pressure, ventilatory frequency and pupil size, patients were also assessed for pain score, sedation score, and nausea and vomiting score (Table 1). Rescue analgesia comprising paracetamol and diclofenac was also available and any usage was noted. On the ward, this monitoring was continued hourly for the first 24 h and 4-hourly for the next 24 h.

VAS scores were assessed daily by the investigators who were unaware of the study drug used and who also noted the number of i.m. injections received, any complications, blood loss into the drains and use of additional 'escape' analgesics or antiemetics for each 24-h period.

Statistical analysis was performed using the Statistical Package for the Social Services for Windows (SPSS, version 6.1). Analysis of variance (ANOVA), chi-square and Kruskal–Wallis tests were used where appropriate. $P<0.05$ was considered statistically significant.

Results

Preoperative data

Of the 75 patients recruited, 65 completed the study. Those not completing included five patients who were admitted to intensive care after operation, one of whom died. Two were withdrawn for being too confused to take part in the postoperative assessments, two had inadequate data compiled and one withdrew herself from the study after consulting with family members. Thus 18 patients in group 1, 22 in group 2 and 25 in group 3 were studied.

Patient characteristics for the three groups were similar (Table 2). There was no significant difference in group size or type of operation performed (supra- or infratentorial). However, group 2 (tramadol 50 mg) was slightly older ($P=0.001$) than the two other groups and there were more females in group 3 (tramadol 75 mg) ($P=0.0278$).

Postoperative recovery data

On discharge from the recovery area, patients were in a similar condition with respect to pain, nausea and vomiting, and sedation. There were no significant differences in the number of analgesic injections required in recovery, or in pain, nausea and vomiting, and sedation scores between the three groups on discharge. The majority (90.8%) of patients had pain and nausea and vomiting scores of 0 or 1 (Table 3). Unfortunately, despite the specified discharge criteria, five patients returned to the ward with pain scores greater than 1: two in the codeine group, two in the tramadol 75 mg group and one in the tramadol 50 mg group.

Postoperative ward data

Pain

On the ward, significant differences in pain scores were observed between the three groups over the first 48 h after operation. Group 1 (codeine 60 mg) had significantly lower pain scores than groups 2 and 3 (tramadol 50 mg and

Table 2 Patient characteristics. ***Group 2 (tramadol 50 mg) was slightly older ($P=0.001$) than the two other groups and *group 3 (tramadol 75 mg) had a higher female to male ratio ($P=0.0278$)

	Age (yr) mean (95% CI)	Sex (M:F)	Operation (supra: infratentorial)
Group 1 ($n=18$), codeine 60 mg	51.0 (49.9–52.1)	8:10	16:2
Group 2 ($n=22$), tramadol 50 mg	54.1 (53.1–55.1)***	11:11	18:4
Group 3 ($n=25$), tramadol 75 mg	52.2 (51.4–53.0)	7:18*	24:1

Table 3 Recovery room data. No significant differences between the three groups

	No. (%) requiring analgesic injection in recovery	Pain score of 0 or 1 (%)	Nausea and vomiting score of 0 or 1 (%)
Group 1 ($n=18$), codeine 60 mg	10 (55.6)	16 (88.9)	16 (88.9)
Group 2 ($n=22$), tramadol 50 mg	9 (40.9)	21 (95.5)	20 (90.9)
Group 3 ($n=25$), tramadol 75 mg	13 (52.0)	22 (88.0)	23 (92.0)

Table 4 Postoperative pain scores and visual analogue scale (VAS) scores (median (range)). ***Group 1 had significantly lower pain scores and VAS scores at 48 h ($P<0.0001$ for both)

	Pain scores	VAS 24 h	VAS 48 h
Group 1 ($n=18$), codeine 60 mg	0 (0–2)***	30.5 (10–85)	10.5 (0–40)***
Group 2 ($n=22$), tramadol 50 mg	1.0 (0–2)	35.0 (0–72)	17.0 (0–50)
Group 3 ($n=25$), tramadol 75 mg	1.0 (0–3)	34.0 (0–90)	15.5 (0–50)

Table 5 Number of analgesic injections received by patients after operation on the ward. Values are median (range) per 24-h period. **Group 1 had significantly fewer injections in both the first and second 24-h periods ($P<0.01$ for both)

	Median No. of analgesic injections during 1st 24 h	Median No. of analgesic injections during 2nd 24 h
Group 1 ($n=18$), codeine 60 mg	2 (0–4)**	0.5 (0–5)**
Group 2 ($n=22$), tramadol 50 mg	2.5 (1–6)	1 (0–4)
Group 3 ($n=25$), tramadol 75 mg	3 (1–6)	1 (0–11)

75 mg, respectively) ($P<0.0001$) (Table 4). Further analysis confirmed that these significant differences occurred in both males and females ($P<0.0001$ for both). Multiple regression analysis confirmed a negative relationship between age and pain. That is, older patients had lower pain scores ($P<0.0001$). There was no significant difference in pain scores between those patients who underwent supra- or infratentorial craniotomy. No patient in the infratentorial group recorded pain scores of 2 or 3 (moderate or severe pain).

There was no significant difference in VAS scores at 24 h between the three groups ($P=0.096$). However, group 1 (codeine 60 mg) had significantly lower VAS scores at 48 h (median 10.5 compared with 17.0 and 15.5 for tramadol 50 mg and 75 mg, respectively) ($P<0.0001$) (Table 4).

Group 1 had significantly fewer injections of codeine than the two other groups had of their respective doses of tramadol at both 24 and 48 h ($P<0.01$) (Table 5). Very few patients required additional 'escape' analgesia: three in the tramadol 75 mg group and two in each of the other groups.

Nausea and vomiting

Postoperative nausea and vomiting were significantly more common in group 3 (tramadol 75 mg) ($P<0.0001$) (Table 6). Again, this difference was seen in both males ($P=0.0029$) and females ($P<0.0001$). However, females had significantly higher scores than males ($P=0.019$). Patients receiving tramadol 75 mg were given significantly more additional 'escape' antiemetics than the other groups ($P<0.0001$).

Sedation

There was a significantly greater number of patients in group 3 (tramadol 75 mg) with a high sedation score of 5 compared with the two other groups, and fewer patients who were awake (score of 1) ($P=0.0001$) (Table 7). This was seen in both males ($P<0.0001$) and females ($P<0.0001$). Females had significantly higher sedation scores in all groups ($P<0.0001$).

Neurological observations

Pupil size was significantly smaller in the codeine group and larger in the tramadol 75 mg group ($P<0.0001$). Group 2 (tramadol 50 mg) had significantly higher ventilatory frequencies than the two other groups ($P=0.0001$).

Cardiovascular observations

Significant differences were observed in cardiovascular variables of the three groups. Higher heart rates, and

Table 6 Nausea and vomiting scores. Values are percentage of each group in each scoring category. ***Group 3 (tramadol 75 mg) had significantly higher scores over the 48-h period ($P<0.0001$)

	0 None (%)	1 Nausea (%)	2 Retching (%)	3 Vomiting (%)
Group 1 ($n=18$), codeine 60 mg	88.3	9.4	0.7	1.5
Group 2 ($n=22$), tramadol 50 mg	92.6	5.4	1.5	0.5
Group 3 ($n=25$), tramadol 75 mg	82.7	10.8	2.5***	4.0***

Table 7 Sedation scores. Values are percentage of each group in each scoring category. ***Group 3 (tramadol 75 mg) had significantly fewer patients with the lowest sedation score and significantly more with a high sedation score ($P=0.0001$)

	1 Awake (%)	2 Agitated (%)	3 Intermittently awake (%)	4 Roused by voice (%)	5 Roused by pain (%)	6 Unrousable (%)
Group 1 ($n=18$), codeine 60 mg	62.4	3.0	18.3	16.3	0	0
Group 2 ($n=22$), tramadol 50 mg	74.1	3.9	8.0	13.9	0	0
Group 3 ($n=25$), tramadol 75 mg	57.5***	7.3	19.1	14.3	2.7***	0

Table 8 Postoperative cardiovascular observations over 48 h (mean (95% CI)). ***Group 2 (tramadol 50 mg) had significantly higher mean heart rates (HR), systolic (SAP) and diastolic (DAP) arterial pressures than the two other groups ($P<0.0001$ for all)

	HR (beat min^{-1})	SAP (mm Hg)	DAP (mm Hg)
Group 1 ($n=18$), codeine 60 mg	75.2 (74.1–76.3)	137.1 (135.6–138.6)	73.2 (72.4–74.0)
Group 2 ($n=22$), tramadol 50 mg	80.5 (79.3–81.7)***	141.3 (139.8–142.8)***	77.9 (77.0–78.8)***
Group 3 ($n=25$), tramadol 75 mg	76.6 (75.6–77.6)	136.2 (134.9–137.5)	74.4 (73.6–75.2)

Table 9 Postoperative blood loss into the drains (mean (95% CI)). ***Group 2 (tramadol 50 mg) had significantly less blood loss into the drains ($P<0.0001$)

	Blood loss in drain (ml)
Group 1 ($n=18$), codeine 60 mg	179 (164–193)
Group 2 ($n=22$), tramadol 50 mg	96 (86–105)***
Group 3 ($n=25$), tramadol 75 mg	171 (160–181)

systolic and diastolic arterial pressures ($P<0.0001$ for all) were seen in group 2 (tramadol 50 mg) over 48 h (Table 8). There were no significant differences in cardiovascular variables between groups 1 (codeine 60 mg) and 3 (tramadol 75 mg).

Standard postoperative observations revealed further differences between the three groups: group 2 (tramadol 50 mg) had significantly less blood loss into drains ($P<0.0001$) (Table 9).

Discussion

Postoperative pain after craniotomy is often considered to be moderate, not requiring large doses of opioid analgesia. This study confirmed that, although most patients suffered some pain, pain scores were in the range 0–2 (no pain, mild or moderate) in the majority of patients (92.8%) and in only 7.2% of cases were scores of 4 (severe pain) recorded. The quality of analgesia provided by codeine has been questioned because of the indirect effects of its metabolites.[3] Other more potent opioids, such as morphine, have also been avoided because of their side effects, specifically sedation, respiratory and cardiovascular depression, and nausea and vomiting. Tramadol offers potential advantages over all opioids by having weak opioid effects and thus avoiding most of these side effects.[10–12] In producing analgesia by multiple pathways,[8 9] tramadol has been shown in several studies to provide good postoperative analgesia after other types of procedure such as laparotomy[15] and laparoscopy.[16] Therefore, it would be expected to be a suitable analgesic after cranial surgery. Two doses of tramadol were used because of the lack of a definitive dose described in the British National Formulary and the fact that other studies using tramadol describe a dose range of 50–100 mg.

In this study, there was little difference in patient characteristics in each group and patients were comparable before discharge from the post-anaesthetic care unit (i.e. relatively pain free with little nausea and vomiting). This provided similar groups on which to compare the efficacy of postoperative analgesics. On the ward, there were significant differences between the three groups. Codeine provided superior pain relief: postoperative pain scores of patients receiving codeine were consistently lower than in those patients receiving either of the doses of tramadol. The codeine group also required fewer i.m. injections. In fact, the larger dose of tramadol appeared to have an antanalgesic effect not previously described and could be a result of its partial agonist effect or possibly increased sedation in this group, making pain assessment and/or interpretation difficult. The poor results with tramadol 75 mg are surprising considering that this dose is said to have a potency comparable with pethidine 100 mg.[10]

There were no sex differences in pain scores but older patients reported less pain, a finding which is consistent with the reduction in analgesic requirements reported previously in elderly patients.[17] Our study demonstrated no difference in pain scores for patients undergoing infra- or supratentorial operations. No pain scores of 2 or 3 (moderate

or severe pain) were recorded by patients undergoing infratentorial operations, contrary to the view that infratentorial procedures are usually more painful. However, the number of patients who underwent infratentorial operations was small (seven in total; two in group 1, four in group 2 and one in group 3) and these patients were nursed in a high dependency unit, with a smaller nurse to patient ratio, and hence may have received more prompt analgesia when requested.

Nausea and vomiting scores were significantly higher in those patients receiving the larger dose of tramadol (75 mg). Tramadol has been demonstrated to cause an incidence of postoperative nausea and vomiting of up to 30–35% in previous studies[10] and the larger dose would be expected to cause more side effects. Females suffered more nausea and vomiting than men in all groups, which is a consistent finding in many studies on postoperative vomiting.[18] In the tramadol 75 mg group, significantly more patients had a high sedation score and fewer were assessed as being 'awake', although the range of scores in all groups was wide. Clinically, those patients assessed as being rousable only by pain had received tramadol 75 mg. This is not consistent with the conclusion of Lehmann, Horrichs and Hoeckle[12] that tramadol was unsuitable for peroperative analgesia because its lack of sedative effects could increase the risk of awareness.[12] However, this was later disputed by Coetzee, Maritz and Du Toit[19] and our findings support the latter group's conclusions.

Although statistically significant differences were found in ventilatory frequencies and cardiovascular variables between the three groups, the tramadol 50 mg group having higher rates and pressures throughout, these were not clinically significant. Importantly, no patient experienced respiratory depression.

There is no obvious explanation for the significantly lower blood loss into the drains in the tramadol 50 mg group. This finding is surprising because the higher arterial pressures in this group would be expected to be associated with greater blood loss. Both the higher ventilatory frequencies and greater blood loss in the tramadol 50 mg group could have been caused by greater pain or purely by chance.

In summary, although it may have been expected that tramadol would have potential benefits for postoperative analgesia after intracranial surgery, we have demonstrated that it conferred no benefit over codeine phosphate in such patients. Codeine provided significantly better postoperative pain relief than tramadol. The higher dose of tramadol caused more sedation and nausea and vomiting, and cannot be recommended after this type of surgery.

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