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Original Research

Managing Postoperative Analgesic Failure: Tramadol Versus Morphine for Refractory Pain in the Post-Operative Recovery Unit

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Abstract

Objective. This study aimed to discover whether co-analgesia with tramadol or additional morphine was more effective for patients who still had severe pain despite being given 10 mg intravenous morphine in the post-anesthesia care unit (PACU).

Methods. All eligible patients were consented and recruited to the trial pre-operatively, but only a small subgroup – whose pain was not successfully controlled (pain score 6/10 or more) after receiving 10 mg of morphine in the PACU—were then randomized to enter the trial and receive, in a double blinded fashion, the analgesic study drug; which consisted of either a further 10 mg of morphine, or 100 mg of tramadol, titrated intravenously to control their pain. The groups were compared as to: the time to readiness for discharge, the patient's pain scores over time, and the presence of side effects.

Results. There was no statistically significant difference in any of the outcomes measured. The time to readiness for discharge from PACU was 119 minutes in the morphine group and 120 minutes in the tramadol group. However in approximately half the cases who entered the trial (i.e., where pain had not been controlled with the pre-enrollment baseline 10 mg of morphine in PACU) neither a further 10 mg of morphine nor 100 mg of tramadol effectively relieved the patient's pain.

Conclusions. We found no difference between additional morphine and co-analgesia with tramadol in this study. Patients who don't respond to reasonable doses of opioids in PACU are very likely to be unresponsive to further opioids, and other non-opioid analgesic techniques (such as regional anesthesia) should be considered early in this group of patients.

Key Words. Morphine; Pain; Postoperative; Tramadol

Introduction

Despite anesthetists' best efforts, a proportion of patients emerge from anesthesia with severe post-surgical pain in the Post-Anesthesia Care Unit (PACU). In a recent survey of PACU problems, 33.9% of all anesthetist attendances in the PACU were related to pain [1]. Ongoing pain in the PACU causes a great deal of distress for the patients themselves, and all involved with

their care. Severe pain delays discharge from PACU. Being able to identify these patients quickly and to offer them effective treatment would have major benefits—less time spent in severe pain, less time spent in PACU, and fewer treatment related side effects. A recent analysis of the closed claims database looking at the incidence of serious respiratory depression associated with acute pain treatment, found that at least 13% of events occurred within 2 hours of PACU discharge, and of the claims analysed over half resulted in death and 22% in severe brain damage [2]. Co-analgesia with tramadol may reduce the incidence of respiratory depression while still offering effective analgesia [3,4].

Given that there is only a relatively small overlap between the mechanisms of action of the two drugs we are studying, and the possibility that tramadol is the more effective agent against neuropathic pain [5], there are reasonable grounds to propose that the two agents would work well together. However, the available literature reaches conflicting conclusions. Marcou et al. demonstrated in ASA 1–2 patients having moderately painful surgery that the combination of morphine and tramadol in the post-operative period was infra-additive, i.e., each agent alone was more efficacious than the combination of the two agents [6]. Two additional studies, one following total knee arthroplasty and one following neonatal surgery, showed no benefit from adding tramadol to the post-operative analgesic regimen [7,8]. Countering this, Webb et al. showed an increase in analgesic efficacy and no increase in side effects when tramadol was added to a morphine PCA for post-operative analgesia following major abdominal surgery [9]. There is also some evidence from the settings of chronic osteoarthritis pain and cancer pain that adding tramadol to a strong opioid improves analgesic efficacy [10,11]. A recent meta-analysis looking at the benefit of adding tramadol to opioid based analgesic regimens found that tramadol produced a 7 mg morphine sparing effect but no reduction in side effects. However, as stated by the authors "the evidence available for this meta-analysis was weak" and hampered by "small sample sizes at single institutions" [12].

In our institution the most common approach to the problem of refractory pain in the PACU, is to titrate intravenous morphine up to an additional 10 mg over and above the opioids that the patient received in theatre. A proportion of patients are still in severe pain after this further dose of morphine. Our PACU nurses have noticed that these patients with relatively "opioid resistant" pain often respond well to tramadol with quite rapid reduction in levels of pain. Is this an effect of tramadol, or is the administration of tramadol merely coinciding with the peak effect of the morphine that they have already received? The aim of this study was to explore this issue by comparing the relative effectiveness of either further morphine or the addition of tramadol, in patients who were still in severe pain after receiving 10 mg of intravenous morphine in PACU.

Unlike previous studies this is not a study of whether tramadol reduces morphine requirements, or a study of which of the two drugs is more efficacious for post-operative pain. This is a study of whether tramadol performs better than more morphine in the refractory pain situation, where the patient has effectively "failed" analgesia from usual post-operative rescue doses of morphine.

Our null hypothesis was that more morphine or tramadol would be equally efficacious for patients with refractory pain in the PACU.

Methods

Ethics committee approval was gained from the Northern Y ethics committee prior to commencement of the study. The trial was registered with the Australian and New Zealand Clinical Trials registry, prior to commencement of the study (ACTRN12611001220954). All ASA 1–3 patients undergoing surgery who provided informed consent were eligible to enter this trial. Exclusions were patients with a chronic pain diagnosis, long term opioid use, chronic renal failure, allergy to either tramadol or morphine, history of poorly controlled epilepsy, or on long term selective serotonin re-uptake inhibitors that may increase the risk of serotonin syndrome when combined with tramadol.

All patients were approached and written informed consented was obtained prior to surgery over two time periods (November 2012–February 2013 and September 2013–February 2014) where employment of research staff allowed us to approach eligible patients having elective or non-elective surgery between Monday and Friday, who were present in the hospital and able to be approached for consent between the hours 8:00 am to 5:00 pm. There were no significant changes of practice or anesthetic staffing during these two periods in our institution.

Anesthetic and intra-operative analgesic techniques were solely at the discretion of the attending anesthetist. The vast majority of patients received a general anesthetic with opioid based analgesia. Clearly procedures done solely under neuruaxial or major plexus block anesthesia would be unlikely to have a pain score 6 or above in the PACU. However, there was one patient in the study who had spinal anesthesia who became eligible for the study.

In PACU all consented patients were offered intravenous morphine titrated up to 10 mg to achieve adequate pain relief. Any patients that received the full 10 mg of morphine and still had a pain score of 6 or more, 5 minutes after the last dose of morphine, were classified as having refractory pain and were then eligible to enter the study. At this point they were randomized by concealed envelope to either study group one or two. Study group one received more morphine, titrated up to a further 10 mg, and study group two received tramadol titrated

up to 100 mg intravenously. Each morning the study drugs were drawn up by one of the investigators and left in the controlled drug safe. Each drug was diluted up to 10 ml in identical syringes labelled either "Study Drug 1" or "Study Drug 2." When a consented patient became eligible for the study, having received 10 mg of morphine and still having a pain score of 6 or above, the attending PACU nurse then opened the randomization envelopes and administered the required study drug. The PACU nurse and the patient were blinded to the contents of the syringe. The PACU nurse recorded the pain score at entry to the study and after the study drug had been administered, the time over which the study drug was administered, the total time spent in PACU, and the presence of any side effects during study drug administration. The rate at which the study drug was administered was at the discretion of the PACU nurse, and the individual dose was 1–2 ml of the study medication at a time.

If, at the end of the study drug titration, the patient's pain score was greater than mild (3/10 pain), then their management returned to their treating anesthetist, and there were no restrictions on what further treatments could be administered. Table 1 describes patients who were not eligible for discharge at the end of the study drug titration.

Additional information recorded was whether the patient was eligible for discharge at the end of the study drug administration (patient requires 13/14 or 14/14 on the post-anesthetic recovery score (PARS) score to be discharged, Table 2), the type of operation, the intraoperative analgesia they had received, and the intraoperative and postoperative anti-emetics that they had received.

The primary outcome measure was time to readiness for discharge from PACU. This was chosen as the primary outcome measure as it gives an overall impression of the benefit to the patient. Readiness was determined by PARS scoring and this scoring system is sensitive to both the analgesia and to the analgesia's likely side effects. (Note that it was the time at which the patient was *eligible for discharge*, not the *actual time of discharge*—which is often affected by many other irrelevant institutional factors). Secondary outcomes were readiness for discharge at the end of study drug titration, pain scores at entry and end of the study drug administration, and the presence of nausea or vomiting.

Pain was assessed on a 11-point numerical rating scale (0 = no pain, and 10 = worst pain imaginable), and nausea and vomiting was measured on a combined 7 point scale (0–3 for vomiting or dry retching, and 0–3 for nausea) which has been used in previous studies [13].

The primary endpoint was powered to detect a 30% reduction in PACU stay, which was arbitrarily deemed to be clinically significant. The PACU stay is recorded electronically in our institution for each patient who enters recovery. Their time of admission, the time when they are ready for discharge, and the time that they actually leave PACU is recorded. The time to readiness for discharge was extracted from this electronic data record.

Graphpad statmate (GraphPad Software, Inc., La Jolla, CA, USA) was used for the power calculation. Using an alpha value of 0.05 and a beta value of 0.8 yielded a sample size of 43 patients for each group. Accounting for potential drop outs and incomplete data collection we aimed to enroll 50 patients in each group for a total of 100 patients.

Statistical analysis of the results was done with Graphpad Quick calcs package (GraphPad Software, Inc., La Jolla, CA, USA) and NCSS 2007 (NCSS, Kaysville, UT, USA). Data are presented as mean (±standard deviation). Categorical data were compared with Fisher's exact test and continuous numerical data were compared, after checking for normality with a two-tailed Student's *t*-test, or a Mann-Whitney U test if the data was not normal distributed. A two-way analysis of variance (ANOVA) was used to determine if there was any interaction between surgical type and outcome variables.

Results

During the study period, 2,541 patients were screened. Of those, 1,386 patients were eligible and consented to participate, 857 patients were ineligible, and 296 declined to participate. Overall 83 patients (6% of the total recruited) still had a pain score of 6 or greater after 10 mg morphine in PACU and were randomized to receive a study drug. Table 3 shows the surgical subspecialty of the patients receiving a study drug. Of the 100 randomization envelopes, 83 were opened in accordance with the trial protocol and completed the trial appropriately, two envelopes were opened prior to the 10 mg of morphine being given and therefore were excluded, one patient received one ml of study drug (tramadol) before developing a rash and being withdrawn from the study, and 14 envelopes were prematurely opened, or mislaid during the move following rebuilding of the operating theatres (without patient recruitment into the study).

Of the 83 patients with data available for analysis, 43 were in the morphine group and 40 were in the tramadol group. The demographics of these two groups are presented in Table 3. There was a statistically significant difference in the number of orthopedic patients between the groups with a higher number in the tramadol group ($P = 0.01$), otherwise there were no other significant differences between the groups.

There was no difference at all in the primary outcome. The time to readiness for discharge from PACU was 119 minutes in the morphine group and 120 minutes in the tramadol group. There was no difference in pain scores or presence of side effects between the groups, as shown in Table 4.

Table 1 Patients not ready for discharge at the end of the study drug titration

Morphine Group Procedure	Starting pain score	Finishing pain score	Time to readiness for discharge (minutes)
Total hip arthroplasty	10	7	111
Laparoscopic nephrectomy	7	7	122
Laparoscopic hemicolectomy	9	5.5	134
ORIF ankle	8	8	79
Reversal ileostomy	7	6	150
ORIF distal radius	7.5	7	133
Quads rupture repair	7	5	83
Total abdominal hysterectomy	10	10	151
ORIF distal radius	7	8	86
Reversal colostomy	9	7	100
Laparoscopic tubal ligation	9	8	181
Index finger washout	10	10	132
Total hip arthroplasty	8	3.5	208 (sedation not pain delayed discharge)
ORIF tuberosity of humerus	9.5	9.5	220
Washout wrist	7	7	102
Total abdominal hysterectomy	7	6	90
ORIF tibial plateau	8	5	105
Removal metalware mandible	8	4	140
K-wire 5th metatarsal	6	4	122
Vaginal hysterectomy	7	7	130
Total hip arthroplasty	10	9.5	135
Mean	8.1 (+/−1.3)	7.0 (+/−1.9)	129 (+/−38)
Tramadol Group **Procedure**	**Starting pain score**	**Finishing pain score**	**Time until readiness for the discharge (minutes)**
Ureteroscopy	8.5	8	91
Laparoscopic hysterectomy	9	8	180
Tibial nailing	8	8	122
ORIF tibial plateau	7	6	94
ORIF tibial plateau	9	7	88
Tibial nailing	8	7	190
ORIF ankle	7	8	100
ORIF ankle	8	5	83
Shoulder decompression	7	7	120
ORIF patella	7	6	136
Knee arthroscopy and tibial osteotomy	8	8	195
ORIF wrist	10	7	148
Ureteroscopy	8	8	120
Mastectomy and lat.dorsi flap	8	6	127
Total knee arthroplasty	10	9.5	171
ORIF tibial plateau	8	7	168
L4-L5 fusion and instrumentation	8	5	112
Total knee arthroplasty	9	9	145
ORIF wrist	7	8	208
Mean	8.1(+/−0.9)	7.2(+/−1.2)	137(+/−39)

Table 2 Post anesthetic recovery score: Discharge criteria

Oxygen saturation	
$\geq$ or = 95% on room air	2
$\geq$ or = 94% up to 5L/min O^2	1
$\leq$ 93% when on any O^2	0
Airway	
Maintains own airway, coughs freely	2
Spontaneous breathing, may have abnormal rate	1
Requires airway support, dyspnoea	0
Vital signs, adults	
+/− 20% or pre-op SBP	2
+/− 20% -40% pre-op SBP	1
>+/− 40% pre-op SBP	0
Level of consciousness	
Awake/drowsy/rouses easily	2
Rouses to physical touch	1
Rouses to painful stimuli/unconscious	0
Motor movement (in comparison to pre-op state)	
Able to move all 4 limbs, normal power & holds head off the pillow for 5 seconds	2
Able to move 2 limbs with normal power	1
No voluntary movement	0
Pain score	
Patient pain score 0–3	2 (none to slight)
Patient pain score 4–5	1 (slight to mild)
Patient pain score 6–10	0 (mod to severe)
Post operative nausea and vomiting	
No to slight nausea and no vomiting	2
Transient nausea with vomiting	1
Persistent nausea and vomiting	0

Table 3 Demographic data and surgical subspecialty origin of study patients

	Morphine group	Tramadol group	
Age (years)	42.7(±15.1)	43.7(±14.3)	$P = 0.58$
Gender	M:25 F:18	M17: F:23	$P = 0.19$
Orthopedic	18 (41%)	28 (70%)	$P = 0.014$
General	8 (19%)	3 (7.5%)	$P = 0.20$
Gynecology	9 (21%)	6 (15%)	$P = 0.57$
Other	8 (19%)	3 (7.5%)	$P = 0.20$
Total	43	40	83

Intra-operative multimodal analgesia was common in both groups, with 63% of the morphine group and 70% of the tramadol group receiving at least one other class of analgesic other than an opioid. The pattern of use was not different between the two groups with the following used; parecoxib, paracetamol, ketamine, clonidine, local or regional block (listed in decreasing frequency of use). In the morphine group, one patient received a paravertebral block for thoracic surgery and one patient received a femoral nerve block for a total hip joint replacement. No patients in the tramadol group received a regional block.

Antiemetic use was common and is described in Table 5.

Of the orthopedic patients recruited, foot and ankle surgery made up 13 of the 46 patients recruited and wrist surgery made up a further nine of the 46 patients recruited. There was no significant effect of drug choice or surgical type (orthopedic vs non-orthopedic) on starting and ending pain score or drug dose ($P > 0.4$, ANOVA).

Discussion

In designing this study we attempted to minimize any modification or restriction on clinical practice so that the results obtained reflected "real world" conditions. We needed to be able to recruit easily: Only a minority of patients recruited would end up being randomized to receive the study drug as the majority of patients would respond to the normal PACU analgesic regimen and thus would not reach the endpoint of "severe pain despite 10 mg of morphine given in PACU."

Table 4 Pain scores, drug volume, and incidence of side effects in the two study groups

	Morphine	Tramadol	*P* value
Time in PACU (minutes)	119 (±32)	120.4 (±35)	0.85
Time in study (minutes)	31.7 (±13.2)	30.0 (±11.4)	$P = 0.52$
Time in recovery before starting study (minutes)	45.7 (±17.8)	47.1 (±15.5)	$P = 0.72$
Pain score (start)	7.7 (±1.3)	7.6 (±1.1)	0.85
Pain score (end)	5.2 (±2.6)	5.5 (±2.2)	0.57
Nausea and vomiting score	0.35 (±0.53)	0.40 (±1.06)	0.78
Ready for discharge at end of study drug titration	22/43	21/40	1.0
Average volume of study drug given	8.5 (±2.6)	8.65 (±2.2)	0.8
Number of patients receiving all 10 ml of study drug	30/43	27/40	1.0

PACU = post-anesthesia care unit.

Table 5 Antiemetic use in the study groups

	Morphine group	Tramadol group	*P* value
Intraoperative use of antiemetics	31/43	27/40	0.81
Antiemetic given in PACU	16/43	10/40	0.25
Ondansetron used as antiemetic	20/43	13/40	0.26
Ondansetron given intraoperatively	9/43	10/40	0.79
Ondansetron given post-operatively	12/43	4/40	0.052
Ondansetron given both intraoperatively and postoperatively	1/43	1/40	1.0

PACU = post-anesthesia care unit.

We found no difference in the time to readiness to discharge from PACU or the magnitude of the pain scores, when PACU patients with high pain scores, persisting after 10 mg of intravenous morphine, were treated either with more morphine or with tramadol. We accepted the null hypothesis. Further we note that—in patients who have already received the usual PACU rescue dose of 10 mg morphine—additional morphine or tramadol was relatively ineffective. The study drug only reduced pain scores to a point where discharge from the recovery room was possible in about 50% of cases.

Of the patients who were not able to be discharged at the end of the study drug titration, only two in the morphine group were not able to be discharged for reasons other than high pain scores (both had delayed discharges due to sedation). All of the patients in the tramadol group who were not able to be discharged at the end of the study drug titration, had high pain scores as the reason for not being able to be discharged.

These are important findings. The anecdotal observation that some non-responders to morphine analgesia respond to tramadol is likely to be erroneous in the context of our surgical population. The proportion of patients who have difficult-to-control pain in our PACU is approximately 6%. This value is in keeping with the 9.4% incidence found in another study in orthopedic and general surgical patients [14]. The difference between this rate and our rate may be related to the wider range of surgical specialities involved in our study.

Our study was powered to detect a 30% difference in the primary endpoint. We felt that this magnitude of difference would have clinical significance, i.e., if the tramadol had been superior we would have recommended its use in place of more morphine, and conversely, in our opinion, the risk of missing a smaller difference due to inadequate power did not justify a larger trial. An *a posteriori* analysis of the data indicates that a sample size of 40 in each group was adequate to show a 22-minute difference in PACU stay (which is probably a clinically significant difference). To show a 10-minute difference in PACU stay, 200 patients would have been needed in each group. A sample size of 1,000 patients in each group would have been able to show a 4-minute difference in PACU stay (all calculations made with 80% power and alpha value of 0.05). Therefore we are unable to rule out a small difference between the groups, but it is unlikely that there was a clinically significant difference between the groups.

The most crucial finding here is not that the study drugs were *equally effective*; it is that they were *often ineffective*. Half of all patients who had difficult-to-treat pain after 10 mg of morphine, did not obtain adequate analgesia from the study drug. It is hard to recommend continuing with opioid type medications in this situation.

Adequate analgesia may be achieved more quickly and more safely by pursuing non-opioid forms of analgesia in patients who still have high pain scores after 10 mg morphine in PACU.

Effectively the 10 mg of morphine in PACU selected a group of patients with difficult-to-control pain rather than a group of patients who had had major surgery. At present we have limited ability to predict those patients who will have intractable pain in the early post-operative period, or ongoing pain in the months following surgery. Work is this area tends to detect psychological factors that can predict post-operative pain or focus on genetic influences that may alter drug efficacy, but as yet we cannot predict who will respond well to opioid treatment. There is a clear need to consider a more effective approach to treating pain in these patients. This study model has potential for use in further studies: exploring the individual mechanisms and pharmacogenetics of analgesia; comparing other analgesic modalities; and following non-responders post-operatively to look at changing pain levels over weeks to months.

We expected to find a reasonable association between the severity of the surgery and the post-operative pain, and to see numerous laparotomies, thoracotomies, knee and shoulder surgeries in the study group. Instead, the 83 study patients did not appear to have more "severe" surgery than those whose pain was managed with the initial dose or morphine. The study group contained seven people who had had total hip joint replacements, and only one patient who had had a total knee joint replacement. This is at odds with ratio of hip-to-knee joint operations performed and with the traditional belief that knee surgery pain is more difficult to manage. The two longest stays, both due to poorly controlled pain were an open reduction and internal fixation of the humeral tuberosity and an ORIF wrist (220 and 208 minutes, respectively), not what would normally be considered painful surgeries.

There are a number of difficulties and weaknesses in this study which are reflective of real world practice. The anesthetic technique was not controlled, so patients arrived in PACU with variable levels of analgesic medication on board. However, ensuring that all patients had 10 mg morphine titrated prior to using the study drug should have evened out much of this variability. The fact that only 6% of patients recruited entered the study suggests that overall intra-operative analgesia was reasonably attended to.

The loss of 14 randomization envelopes is a concern. As one might expect from an adequately randomized trial, the lost envelopes where evenly divided between the two groups and despite the lost envelopes the predetermined number of subjects was achieved in one group and very nearly achieved in the other group.

The use of ondansetron was not controlled during the study and ondansetron has been shown to significantly reduce the efficacy of tramadol [15,16]. It was not deemed reasonable to control the intraoperative use of ondansetron as only a small number of patients recruited actually entered the study. In recovery room, ondansetron is frequently used and it was also deemed unreasonable to restrict its use, as this is not the normal situation and the combination of tramadol and ondansetron in the recovery room is likely to be very common.

Despite our randomization process there was a larger proportion of orthopedic patients in the tramadol group than the morphine group. However the two-way ANOVA did not show any effect at all between orthopedic vs non-orthopedic surgery, or any interaction between surgical type and drug group.

Conclusion

In conclusion, this study provides useful information about the treatment, incidence and recovery room characteristics of difficult-to-control post-operative pain. It shows that there is no clear benefit or detriment, to treating difficult-to-control pain with tramadol over morphine, when the patient has already received 10 mg morphine in the recovery room. Further that the additional morphine or tramadol resulted in adequate pain control in only about half of these patients. Some other analgesic adjunctive method should be considered such as a regional anesthetic technique or non-opioid adjuncts such as ketamine or clonidine. Further research needs to be done to fully elucidate the reasons for inadequate analgesic response to opioids and to investigate alternative methods for treatment of refractory pain in the recovery room.

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