

Original article:

PRE-EMPTIVE PARACETAMOL REDUCES INTRA-OPERATIVE OPIOID USE IN PATIENTS UNDERGOING DAY-CASE ONCOLOGIC BREAST SURGERY

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ABSTRACT

Minimization of intra-operative opioid use is an area of ongoing research interest with several potential benefits to the patient. Pre-emptive analgesia, defined as the administration of an analgesic before surgery to prevent establishment of central sensitization of pain, is one avenue that has been explored to achieve this. A retrospective observational study was undertaken to examine the effect of pre-emptive paracetamol on intra-operative opioid requirements. The medical and operative data of 156 patients who underwent day-case wide local excision and sentinel lymph node biopsy with and without regional block surgery at our center between October 2019 and May 2022 was carried out. Data were collected on demographics, total intra-operative and immediate post-operative opioid consumption. 57 patients did not receive pre-emptive paracetamol while 90 did. Baseline characteristics were similar. Our results showed a statistically significant reduction in morphine ($p < 0.029$) and remifentanyl ($p < 0.007$) consumption in patients who received a regional block and pre-emptive paracetamol. Those who did not receive a regional block and were given pre-emptive paracetamol had a decrease in OxyNorm ($p < 0.022$) requirements. A combination of general anesthesia (GA), regional block and pre-emptive paracetamol reduced intra-operative consumption of Fentanyl, OxyNorm, diclofenac, dexketoprofen, and clonidine ($P < 0.001$) when compared to just GA alone. Use of pre-emptive paracetamol in reduction of intra-operative opioid requirements showed promising results but larger studies may strengthen the evidence for this association. A multimodal analgesic approach that utilizes pre-emptive paracetamol can be a viable method to decrease intra-operative of analgesic requirements.

Keywords: Pre-emptive analgesia, opioid-sparing, intra-operative opioids, pain, breast surgery

INTRODUCTION

Opioids have long played a central role in the management of acute and malignancy pain. Their efficacy in the acute setting is offset by a recognized constellation of adverse effects, including nausea, vomiting and constipation (Kim et al., 2020). An increasing trend in their use has been observed globally,

with an associated rise in mortalities and morbidities. Unnecessary use of opioids in patients where suitable alternatives are available and benefits are less likely to outweigh risks has been noted as one of the primary causes of the opioid crisis (Moriarty et al. 2022). In addition, surgery has been described as a risk factor for chronic opioid use, with some papers reporting overuse in opioid-naïve

patients (3–15 %) for prolonged periods (Sun et al., 2016; Jivraj et al., 2020; Moriarty et al., 2022).

The ongoing opioid epidemic in the United States initiated efforts to identify opioid-sparing analgesic regimes in various settings, with over 300 publications on the topic catalogued on PubMed over the past 10 years (Shanthanna et al., 2021). Reducing post-operative opioid use and prescribing has been heavily researched and advocated for (Nuckols et al., 2014; Wetzel et al., 2018; Daoust et al., 2022). However, reducing opioid usage in the peri-operative period remains a novel area of continuing research, with pre-emptive analgesia promoted as a possible way to achieve this aim. Pre-emptive paracetamol administration has been associated with a decrease in opioid consumption 24 hours post-operatively and minimized intra-operative anesthetic requirements, yet its use remains controversial (Ali and Siddiqui, 2012; Fenlon et al., 2013; Khalili et al., 2013; Abdelmageed and Al Taher, 2014; Medina Vera and Novoa, 2016; Ng et al., 2019; Kim et al., 2020). This study examined the impact of pre-emptive paracetamol use on intra-operative opioid requirements in patients undergoing oncologic breast surgery.

METHODS

A retrospective observational case series study was conducted at our hospital from October 2019 to May 2022. Adult females undergoing elective day-case unilateral wide local excision and sentinel lymph node biopsy were included. Patients undergoing bilateral wide local excision with sentinel lymph node biopsy, wide local excision with axillary clearance or a mastectomy with or without an axillary procedure were excluded, as they were patients who had to stay overnight following their procedure.

Data were collected on the patients' demographics, whether or not pre-emptive analgesia in the form of 1 g of paracetamol via the oral route was administered, whether or not a successful regional anesthetic block was administered, and whether or not the patient

required opioids in the intra-operative and immediate (within four hours) post-operative period. Additionally, the agent, dose and route of administration of opioids were documented if it was required, and we collected data about the surgical and anesthetic teams caring for each patient. Statistical analysis was performed using GraphPad Prism 9, version 9.2.0 (GraphPad Software, Inc., San Diego, CA). A one-tailed Fischer's exact test with a confidence interval of 95 % was used in place of the chi-squared test as >20 % of cells in the contingency table had < 5 expected counts. P-values less than < 0.05 were considered significant. This study adhered to the Preferred Reporting of Case Series in Surgery (PROCESS) guidelines (Agha et al., 2018).

RESULTS

A total of 147 consecutive patients were included: the control group (n=57) and the pre-emptive paracetamol group (n=90, intervention group). The mean age was 80 and 79 years, respectively. There was an equal distribution of right and left-sided surgery performed in both groups, and all patients refrained from eating or drinking for at least eight hours before the surgery. All patients in the intervention group received 1 g of pre-emptive paracetamol orally within four hours prior to surgery and none of the patients in the control group did. A regional paravertebral block consisting of 0.75 % ropivacaine 20 ml, 1 % lignocaine 10 ml and dexamethasone 8 g was administered under ultrasound guidance based on the primary anesthesiologist's preference and patient's characteristics.

The peri-operative team included six primary operating surgeons and 14 anesthesiologists. Variable use of pre-emptive analgesia by surgeons was noted (Figure 1); it was shown that surgeons 1 and 4 had the highest rates, 90.7 % and 76.6 %, respectively. Figure 2 displays the anesthesiologists' total number of cases with their use of regional blocks; anesthesiologists 1 and 7 used regional blocks in 90 % and 88.8 % of their cases, respectively. A regional paravertebral block, which

required an additional 30 minutes on average, was administered in 15/57 (26 %) patients in the control group and 79/99 (80 %) patients in the intervention group. In addition, whenever given, a local anesthetic was administered at the time of closure.

Overall, the intra-operative requirements of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids in the intervention group were decreased when compared to the

control group (Figure 3). Patients that received pre-emptive paracetamol with the regional block had decreased Morphine and Remifentanyl requirements with a statistical significance of $p < 0.029$ and $p < 0.007$, respectively when compared to regional block-only patients (Table 1). The remainder of NSAIDs and opioid demands were reduced but were not statistically significant.

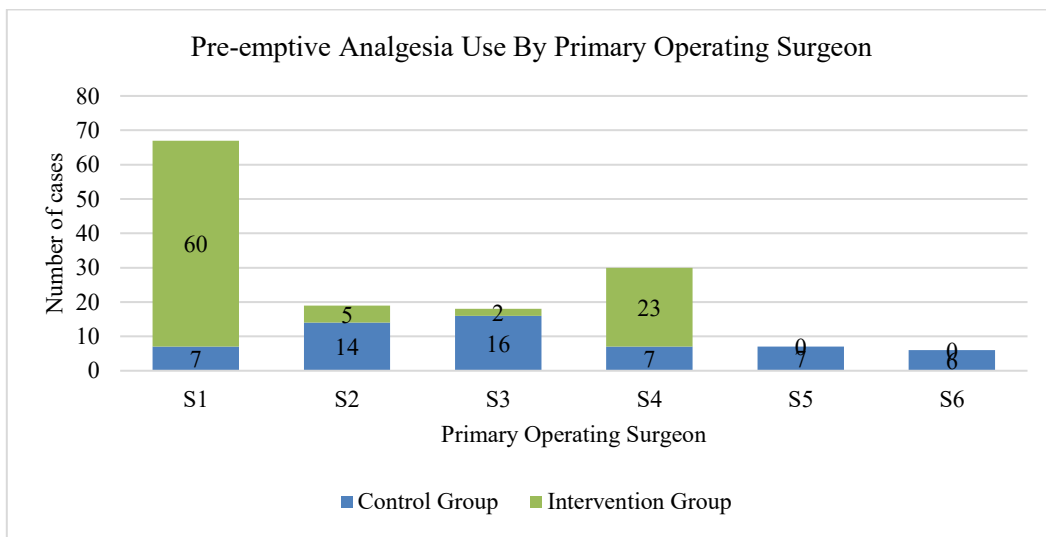


Figure 1: Pre-emptive analgesia use by primary operating surgeon

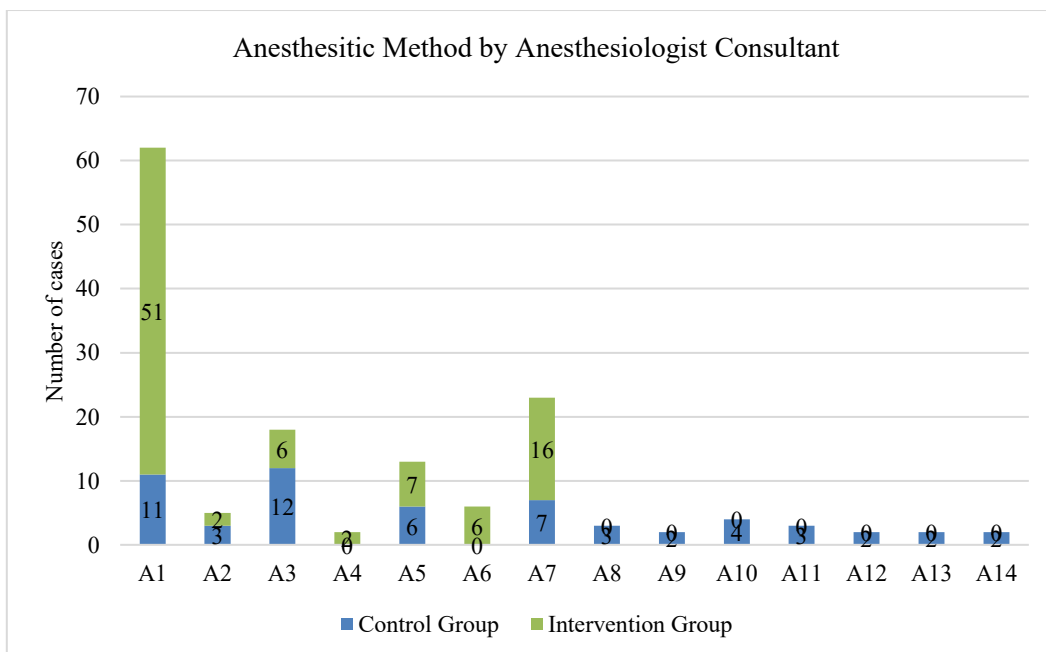


Figure 2: Anesthesiologist consultant cases and their use of regional blocks

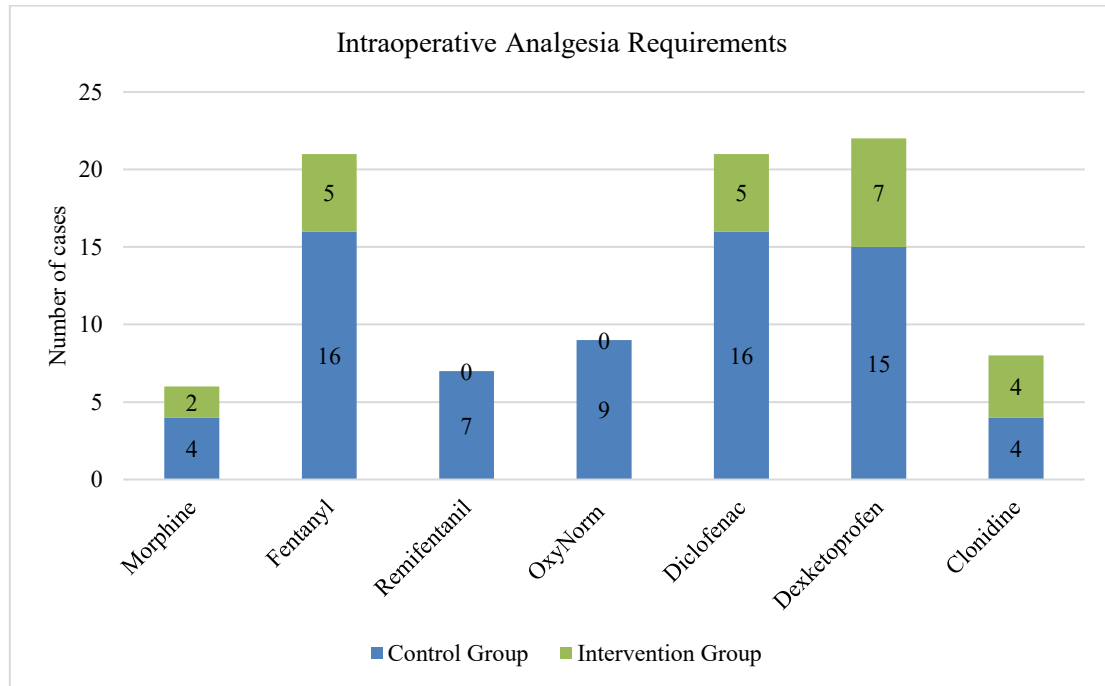


Figure 3: Overall intra-operative analgesia requirements

Table 1: Pre-emptive paracetamol with regional block versus regional block only

Analgesics	Pre-emptive paracetamol + regional block (n=70)		Regional block only (n=15)		p-value
	Number of patients requiring analgesia				
	Number	%	Number	%	
Morphine	0	0.0	2	13.3	0.029
Fentanyl (>150 mcg)	0	0.0	1	6.7	0.176
Remifentanyl	0	0.0	4	26.7	0.007
OxyNorm	0	0.0	0	0.0	>0.999
Diclofenac	1	1.4	1	6.7	0.324
Dexketoprofen	5	7.1	3	20.0	0.144
Clonidine	0	0.0	0	0.0	>0.999

The cohort of patients that received a general anesthetic (GA) without a regional block were compared in Table 2; those that received pre-emptive paracetamol had a reduction in OxyNorm requirements with a p-value of <0.022. The remainder of NSAIDs and opioid requirements decreased but were not statistically significant. The selected group of patients that received both pre-emptive paracetamol and a regional block was compared to the GA-only group (Table 3); The administration of fentanyl (P <0.001), OxyNorm (P <0.001), diclofenac (P <0.001), dexketoprofen (P <0.003), and clonidine (P <0.018), was reduced with a statistical significance as

shown. Overall, immediate post-operative opioid requirements decreased by 1 % in the intervention group (39.4 % vs 40.4 %, P = 0.89). Length of stay was not impacted by opioid use in all our patient cohorts as all day cases were discharged on the same day without any immediate side effects or requirement for anti-emetic or other medications, although we were unable to account for the exact discharge time.

DISCUSSION

The introduction of multimodal analgesia regimens resulted in enhanced pain control,

reduced opioid consumption peri-operatively, expedited post-operative recovery and decreased opioid prescriptions upon discharge. The introduction of pre-emptive analgesia has further strengthened these findings (Elvir-Lazo and White, 2010; Trabulsi et al., 2010; Kim et al., 2020; George et al., 2023). A retrospective study of 60 patients that underwent a robotic-assisted laparoscopic radical prosta-

tectomy investigated the impact of multi-modal analgesia (pregabalin 150 mg, acetaminophen 975 mg, and celecoxib 400 mg) on the intra-operative consumption of opioids. The intervention group (n = 30) had a significant reduction in intra-operative morphine requirements (38.4 ± 2.73 mg vs 49.1 ± 2.65 mg; $P < .01$) (Trabulsi et al., 2010).

Table 2: Pre-emptive paracetamol without regional block versus control group

Analgesics	Pre-emptive paracetamol without regional block (n=20)		Without regional block (n=42)		p-value
	Number of patients requiring analgesia				
	Number	%	Number	%	
Morphine	2	10.0	2	4.8	0.388
Fentanyl (>150 mcg)	5	25.0	15	35.7	0.294
Remifentanyl	0	0.0	3	7.1	0.286
OxyNorm	0	0.0	9	21.4	0.022
Diclofenac	4	20.0	15	35.7	0.169
Dexketoprofen	2	10.0	12	28.6	0.092
Clonidine	4	20.0	4	9.5	0.224

Table 3: Pre-emptive paracetamol with regional block versus control group

Analgesics	Pre-emptive paracetamol + regional block (n=70)		Without regional block (n=42)		p-value
	Number of patients requiring analgesia				
	Number	%	Number	%	
Morphine	0	0.0	2	4.8	0.139
Fentanyl (>150 mcg)	0	0.0	15	35.7	<0.001
Remifentanyl	0	0.0	3	7.1	0.051
OxyNorm	0	0.0	9	21.4	<0.001
Diclofenac	1	1.4	15	35.7	<0.001
Dexketoprofen	5	7.1	12	28.6	0.003
Clonidine	0	0.0	4	9.5	0.018

Paracetamol, a metabolite of phenacetin, is known for its non-opioid analgesic and antipyretic effects. Its mechanism of action remains unclear, but it is accepted that it works centrally and peripherally to inhibit the synthesis of prostaglandin by cyclooxygenases 1 and 2. Additionally, more recent studies revealed that paracetamol functions through the descending serotonergic pathway and spinal 5-HT receptors to prevent central nociception (Karaman, 2016; Medina Vera and Novoa, 2016; Ng et al., 2019). Pre-emptive paracetamol has been extensively researched and shown to reduce post-operative pain scores and opioid consumption (Medina Vera and Novoa, 2016; Ng et al., 2019; Xuan et al., 2021). A prospect study published in 2020 proposed pain management guidelines for oncologic breast surgery based on a systematic review of 749 studies and a meta-analysis of 53 studies. It was recommended to use peri-operative paracetamol for continuous systematic analgesia instead of opioids (Jacobs et al., 2020). Interestingly, a randomized, double-blind, placebo-controlled study of 62 patients revealed that pre-emptive paracetamol decreased sevoflurane requirements intra-operatively (36.2 ± 15 vs 44.9 ± 13.9 ml in the control group; $p = 0.021$) and resulted in a faster post-anesthetic recovery profile (Abdelmageed and Al Taher, 2014). Studies have reported variable results as to whether intravenous and oral route paracetamol peak plasma concentrations are similar. However, the majority of the studies stated that peak plasma concentrations are greater and achieved quicker after intravenous administration rather than oral (Van Der Westhuizen et al., 2011; Langford et al., 2016). On the other hand, some papers argued that the difference between administration routes is insignificant and that the oral route can reduce the additional costs and risks attached to intravenous preparation (Fenlon et al., 2013; Patel et al., 2020).

To our knowledge, our study was one of the first to examine the intra-operative impact of a single dose of pre-emptive paracetamol for elective oncologic day-case breast

procedures. The results revealed a statistically significant reduction in morphine and remifentanyl consumption in patients who received a regional block and pre-emptive paracetamol. Patients who did not receive a regional block and were given pre-emptive paracetamol had a statistically significant decrease in OxyNorm requirements. A combination of GA, regional block and pre-emptive paracetamol demonstrated reduced intra-operative analgesic demands for fentanyl, OxyNorm, diclofenac, dexketoprofen and clonidine compared to GA alone. Certainly, with these results in mind, future research may look at using a combination of pre-emptive non-opioid analgesia and paravertebral block, without any use of intraoperative opiates.

This study was limited by sample size and confined to breast oncologic day-case surgeries. It was retrospective and a single primary surgeon and anesthetist performed most cases; thus, bias and influence cannot be excluded. Furthermore, due to the retrospective nature of the paper, titration of intraoperative opiates to the depth of anesthesia or to any intraoperative hemodynamic parameters were not looked at.

CONCLUSION

In summary, the use of pre-emptive paracetamol to reduce intra-operative opioid requirements showed promising. However, more extensive studies and randomized clinical trials are needed to further explore and examine this relationship. In addition, this review identified that a multimodal analgesic approach that utilizes pre-emptive paracetamol is a viable method to decrease the intra-operative analgesics requirements.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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Author contributions

Conceptualization, methodology – Daniah Alsaadi.

Formal analysis and investigation – Daniah Alsaadi, Lyndon Low, James Ting, Michael Craughwell.

Writing - original draft preparation – Daniah Alsaadi.

Writing - review and editing – Daniah Alsaadi, Lyndon Low.

Supervision – John McDonnell, Karl Sweeney, Aoife Lowery.

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