ORIGINAL ABSTRACT

Policies of Opioid Administration on the First Postoperative Day in German Hospitals: Is there an Association with Patient Reported Outcomes?

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Background and aim: Against the background of the opioid epidemic, the administration of perioperative opioids is being questioned more and more, especially since the evidence for their effectiveness is weak. At the patient level in everyday clinical practice, it is difficult to establish a dose-response relationship for postoperative opioid administration, since opioids are given when needed, thus making opioid treatment not any longer an independent variable. However, an association between opioids and outcomes might be feasible if wards with different opioids policies (liberal to restrictive) are compared. The primary aim of this study was to identify different opioid policies within the German Quality Improvement in Postoperative Pain Management (QUIPS) registry, the German counterpart of PAIN OUT. The secondary aim was to analyse the association between these different opioid policies and pain-related patient reported outcomes (PRO).

Methods: QUIPS provides standardized tools for assessing perioperative pain management and pain-related PROs. For this analysis, we evaluated data between 2009 and 2020. We used cluster analysis to identify specific patterns of institutional opioid administration, *i.e.* the *ward specific opioid policy*. In detail, for each surgical ward and year (if n ≥ 30 patients) we calculated the percentage of opioid administration on the ward within patients with mild (< 4/10), moderate (4 – 6/10) and severe (≥ 7/10) worst pain intensities. These percentages served as basis for the subsequent *k*-means clustering in multiple sub-samples. In secondary analysis, we assessed the association between *opioid policy* and PROs. In the QUIPS database PROs comprise pain intensity (least, worst, during activity; 0-10 numeric rating scale), interference with pain (movement, coughing/taking a deep breath, sleep, mood; yes *vs.* no) and side effects (fatigue, nausea; yes *vs.* no). The items were summarized to form a pain composite score (PCS), ranging between 0 – 10, with lower values indicating better outcomes. Based on the multi-centre structure of the data, we applied mixed models with a random intercept for every participating ward. The PCS served as the dependent variable. The main independent variables were the *opioid policy*, patients'

individual opioid intake on the normal ward (yes *vs.* no) and the interaction of both. Additionally, the model controlled for age (≤ 60 *vs.* > 60 years), sex (male *vs.* female) and chronic pre-existing pain (yes *vs.* no).

Results: Findings from 290,472 adult patients from 748 wards qualified for the analysis. Each year, a median of 24,955 (interquartile range, IQR: 20,508 – 30,179) patients from 237 (IQR: 188 – 285) wards were recruited. The percentage of opioid administration varied considerably between wards (median: 28.5%, IQR: 1 – 60%). Opioid administration was highest in orthopaedic/traumatology patients (median: 43.4%) followed by patients undergoing general surgery (median: 21.9%) and gynaecologic/obstetric surgery (median: 13.3%). Opioids most frequently administered were oxycodone (n = 69,286, 24%), piritramid (n = 25,963, 9%), tramadol (n = 11,539, 4%) and tilidin (n = 11,030, 4%).

We identified a highly stable 3-cluster solution. The first cluster (*liberal opioid policy*, n = 677 wards, 24.5%) was characterized by a high frequency of opioid administration in all sub-groups of pain intensities (median, mild: 71%, moderate: 81%, high: 89%). In the second cluster (*moderate opioid policy*, n = 869 wards, 31.4%) the frequency of opioid administration increased across the sub-groups (median, mild: 24%, moderate: 40%, high: 57%). In the last cluster (*restrictive opioid policy*, n = 1,222 wards, 44.1%) the frequency of opioid administration was generally low over all sub-groups (median, mild: 0%, moderate: 0%, high: 0%).

In a pooled analysis, patients within wards with a liberal opioid policy showed significantly better PCS than patients from wards with a moderate (standardized contrast; 95% confidence interval: -0.12; -0.14 – -0.10) or restrictive opioid policy (-0.19; -0.22 – -0.17). This effect was more evident in patients with opioid intake (liberal *vs.* moderate policy: -0.17; -0.19 – -0.15 | liberal *vs.* restrictive policy: -0.29; -0.32 – -0.26). Furthermore, in patients who did not receive opioids, outcomes were better in wards with a liberal policy compared to wards with a restrictive-policy (-0.10; -0.13 – -0.07). However, the effect sizes were small to medium for all comparisons. In secondary regression models, we found similar results within the three above-mentioned surgical disciplines. Of note, we identified no clinically relevant differences in side effects in tertiary regression models.

Conclusions: In this study, we found that policies for administering opioids after surgery on the ward fell into three clusters liberal, moderate and restrictive policies. The liberal policy was associated with better pain-related PROs and was not associated with higher rates of side effects.

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Policies of Opioid Administration on the First Postoperative Day in German and Austrian Hospitals: Is there an Association with Patient Reported Outcomes?

PWD353


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IN THE **ACUTE POSTOPERATIVE SETTING** WE IDENTIFIED **WARDS WITH LIBERAL, MODERATE** AND **RESTRICTIVE OPIOID POLICIES**.

THE **DIFFERENCES** IN **PATIENT REPORTED OUTCOMES** WERE **NOT CLINICALLY RELEVANT** BETWEEN THESE POLICIES.

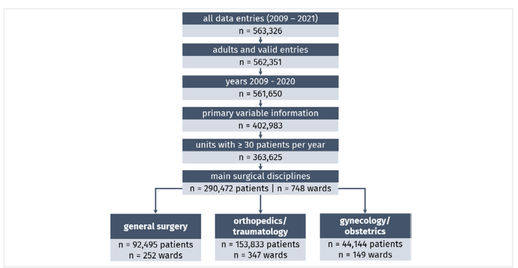

Figure 1. Study flow chart.

Table 1 (left). Number of patients and participating wards over the study period. The majority of wards (n=549/748, 73.4%) contributed data for multiple years (median: 3 years, Q_{1-3}: 1–5 years, maximum: 12 years).

cohort	level	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	overall
total	patients	8,889	24,348	31,461	31,989	34,591	29,752	27,264	25,088	24,822	21,415	17,787	13,068	290,472
	wards	111	228	291	300	314	282	265	245	229	194	171	138	748*
general	patients	3,068	8,872	11,559	10,635	12,198	9,837	7,711	6,101	6,766	6,803	5,446	3,499	92,495
	wards	37	86	105	102	102	96	87	65	69	65	59	45	252*
orthopaedics traumatology	patients	4,351	11,724	14,746	15,971	16,489	15,285	13,444	13,554	14,914	11,644	9,674	8,037	153,833
	wards	52	101	132	139	144	133	129	138	121	94	80	71	347*
gynaecology obstetrics	patients	1,470	3,750	5,156	5,383	5,904	4,630	4,109	3,433	3,142	2,968	2,667	1,532	44,144
	wards	22	41	54	59	68	53	49	42	39	35	32	22	149*

* refers to the number of unique wards (a high number of wards participated over several years)

Table 2. (right) Demographic characteristics of the study sample. Absolute (n) and relative frequencies (%) are shown for the total sample and the surgical disciplines. The majority of patients underwent orthopaedic/traumatology surgery (n=153,833) followed by patients with general surgery (n = 92,495) and gynaecologic/obstetric surgery (n=44,144). The most frequent procedures for the surgical disciplines were laparoscopic cholecystectomy (n = 15,698), total hip replacement (n=22,107) and caesarean section (n=9,730).

In total 2,768 'institutional' data sets (wards per year) were available for clustering (general surgery: n=918; orthopaedics/ traumatology: n=1,334; gynaecology/obstetrics: n=516).

variable	group	n	%	total
age: over 60 years	total	132,121	45.5	290,472
	general	40,276	43.5	92,495
	orthopaedics/traumatology	82,366	53.5	153,833
	gynaecology/obstetrics	9,479	21.5	44,144
sex: female	total	172,683	59.5	290,472
	general	45,761	49.5	92,495
	orthopaedics/traumatology	82,778	53.8	153,833
	gynaecology/obstetrics	44,144	100.0	44,144
chronic pain: yes	total	125,853	43.3	290,472
	general	23,043	24.9	92,495
	orthopaedics/traumatology	96,685	62.9	153,833
	gynaecology/obstetrics	6,125	13.9	44,144
non-opioid (ward): yes	total	204,628	70.5	290,472
	general	64,307	69.5	92,495
	orthopaedics/traumatology	112,805	73.3	153,833
	gynaecology/obstetrics	27,516	62.3	44,144
opioid (ward): yes	total	110,314	38.0	290,472
	general	27,021	29.2	92,495
	orthopaedics/traumatology	70,810	46.0	153,833
	gynaecology/obstetrics	12,483	28.3	44,144

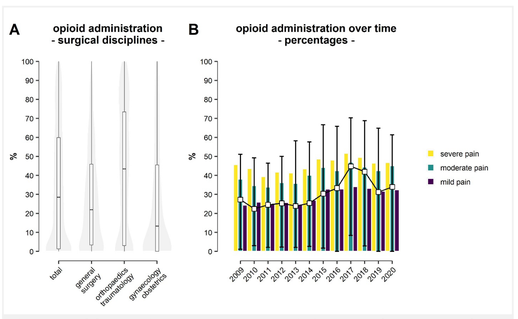

Figure 2: (A) Combined boxplots and violin plots (shaded area) for percentages of opioid administration on the normal ward for the total sample and the surgical disciplines. The shaded area indicates the frequency distribution of wards with a specific percentage of opioid administration. **(B)** Median, first and third quartiles (white squares and capped lines) of opioid administration on the normal ward over the years for participating wards and years. Additionally the median percentage of opioid administration on the normal ward in patients with severe (7–10 NRS), moderate (4–6 NRS) and mild (0–3 NRS) worst pain intensities are shown.
Within all disciplines opioid administration ranged between 0–100%. In median it was highest in orthopaedic/traumatology followed by general surgery and gynaecologic/obstetric surgery.

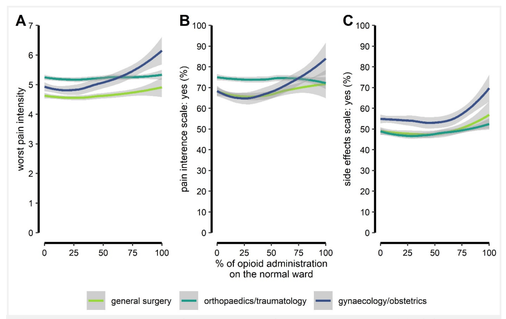

Figure 3: Smoothed plots (Loess Method) for the ward specific (A) average of worst pain intensity, (B) percentage of pain interference and (C) percentage of side effects (y-axis) and the percentage of opioid administration on the normal ward (x-axis). **For general surgery and orthopaedic/ traumatology surgery the ward averages of worst pain intensity and percentages of pain interference scale and side effects showed no substantial differences over the different percentages of opioid administration on the normal ward. In gynaecologic/ obstetric surgery there was an increase in worst pain intensity, pain interference and side effects beginning at ~50% opioid administration. Nonetheless, the absolute differences were small.**

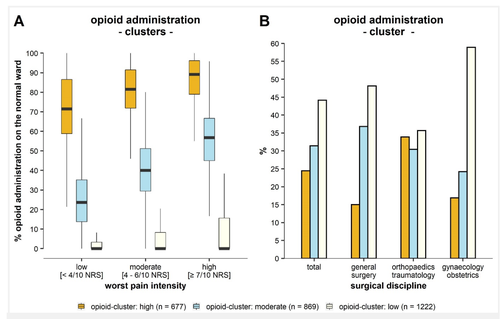

Figure 4: (A) Cluster medians of percentage of opioid administration on the normal ward for patients with low (0–3 NRS), moderate (4–6 NRS) and severe (7–10 NRS) worst pain intensities. **We identified a highly stable 3-cluster solution. The first cluster (*"liberal opioid policy"*, n = 677 wards, 24.5%) was characterized by a high frequency of opioid administration in all sub-groups of pain intensities. In the second cluster (*"moderate opioid policy"*, n = 869 wards, 31.4%) the frequency of opioid administration increased across the sub-groups. In the last cluster (*"restrictive opioid policy"*, n = 1,222 wards, 44.1%) the frequency of opioid administration was generally low. (B)** Distribution of clusters for the total sample and within the surgical disciplines.

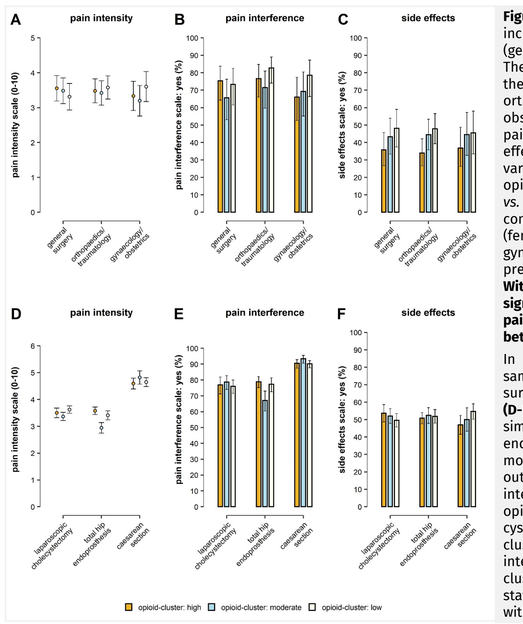

Figure. 5: Estimated marginal means including 95% confidence intervals of the (generalized) mixed regression models. The models were obtained separately for the surgical disciplines (general surgery, orthopaedics/traumatology, gynaecology/ obstetrics). The pain intensity scale **(A)**, pain interference scale **(B)** and side effects scale **(C)** served as dependent variables. The opioid-cluster (institutional opioid administration: low *vs.* moderate *vs.* high). The model additionally controlled for age (≤ 60 *vs.* > 60 years), sex (female *vs.* male, except for the models in gynaecological/obstetric surgery) and pre-existing chronic pain (yes *vs.* no). **Within the disciplines, we found no significant differences for pain intensity, pain interference and side effects between the opioid-clusters.**

In sensitivity analyses we applied the same approach to the most frequent surgical procedure within every discipline **(D-E)**. For all procedures we identified similar 3 cluster solutions. For total hip endoprosthesis, patients within the moderate cluster showed better outcomes for pain intensity and pain interference compared to the other opioid-clusters. For laparoscopic cholecystectomy, patients in the moderate cluster showed better outcomes for pain intensity compared to the other opioid-clusters. None of the other contrasts were statistically significant (p-values adjusted with the Tukey method).

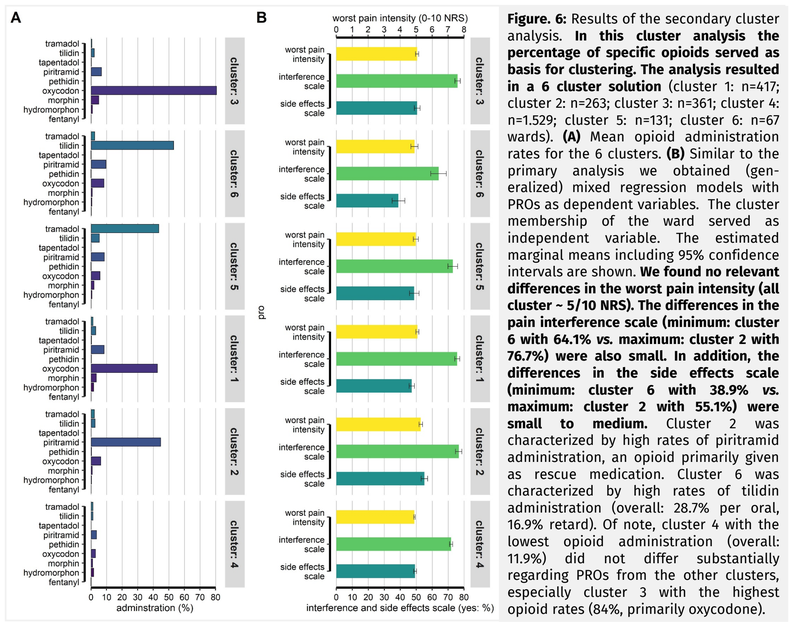

Figure. 6: Results of the secondary cluster analysis. **In this cluster analysis the percentage of specific opioids served as basis for clustering. The analysis resulted in a 6 cluster solution** (cluster 1: n=417; cluster 2: n=263; cluster 3: n=361; cluster 4: n=1.529; cluster 5: n=131; cluster 6: n=67 wards). **(A)** Mean opioid administration rates for the 6 clusters. **(B)** Similar to the primary analysis we obtained (generalized) mixed regression models with PROs as dependent variables. The cluster membership of the ward served as independent variable. The estimated marginal means including 95% confidence intervals are shown. **We found no relevant differences in the worst pain intensity (all cluster ~ 5/10 NRS). The differences in the pain interference scale (minimum: cluster 6 with 64.1% *vs.* maximum: cluster 2 with 76.7%) were also small. In addition, the differences in the side effects scale (minimum: cluster 6 with 38.9% *vs.* maximum: cluster 2 with 55.1%) were small to medium.** Cluster 2 was characterized by high rates of piritramid administration, an opioid primarily given as rescue medication. Cluster 6 was characterized by high rates of tilidin administration (overall: 28.7% per oral, 16.9% retard). Of note, cluster 4 with the lowest opioid administration (overall: 11.9%) did not differ substantially regarding PROs from the other clusters, especially cluster 3 with the highest opioid rates (84%, primarily oxycodone).

BACKGROUND AND AIMS

Against the background of the opioid epidemic, the administration of perioperative opioids is being questioned more and more, especially since the evidence for their effectiveness is weak. At the patient level in everyday clinical practice, it is difficult to establish a dose-response relationship for postoperative opioid administration, since opioids are given when needed, thus making opioid treatment not any longer an independent variable. However, an association between opioids and outcomes might be feasible if wards with different opioids policies (liberal to restrictive) are compared. The primary aim of this study was to identify different opioid policies within the German Quality Improvement in Postoperative Pain Management (QUIPS) registry, the German counterpart of PAIN OUT. The secondary aim was to analyse the association between these different opioid policies and pain-related patient reported outcomes (PROs).

METHODS

- QUIPS provides standardized tools for assessing perioperative pain management and pain-related PROs. For this analysis, we evaluated data between 2009 and 2020 (**see Figure 1)**.
- We used cluster analysis to identify specific patterns of institutional opioid administration, *i.e.* the *ward specific opioid policy*. In detail, for each surgical ward and year (if n ≥ 30 patients) we calculated the percentage of opioid administration on the ward within patients with low (< 4/10 numeric rating scale , NRS), moderate (4 – 6/10 NRS) and severe (≥ 7/10 NRS) worst pain intensities. These percentages served as basis for the subsequent *k*-means clustering in multiple sub-samples.
- In secondary analysis, we assessed the association between *opioid policy* and PROs. In the QUIPS database PROs comprise pain intensity (least, worst, during activity; 0-10 NRS), interference with pain (movement, coughing/taking a deep breath, sleep, mood; yes *vs.* no) and side effects (fatigue, nausea; yes *vs.* no). The **intensity scale** was defined as average of the intensity items. The **pain interference scale** and **side effects scale** was considered as positive, if patients answered one of the interference or side effects items with "yes", respectively.
- Based on the multi-centre structure of the data, we applied (generalized) mixed regression models with a random intercept for every participating ward per year. Models were obtained separately for the main disciplines (general surgery, orthopaedics/traumatology, gynaecology/obstetrics) and pain intensity, pain interference and side effects (details **Figure 5**).
- In sensitivity analyses we applied the same clustering approach and the associative analyses to the most frequent surgical procedures of the three surgical disciplines (details **Figure 5**).
- In the secondary cluster analysis we followed a similar approach. Here, cluster analysis was based on the percentages of specific opioids (details **Figure 6**).

MAIN RESULTS

- **Figure 1** and **Table 1** present the **study flow chart** as well as the **patient and ward numbers**. The **demographic characteristics** are shown in **Table 2**.
- In the total sample the **median percentage of patients receiving at least one dose of opioids on the normal ward was 28.5 %** (Q_{1-3}: 1.3 – 60.0%). In orthopaedic/traumatology wards, percentage was highest (43.4%, Q_{1-3}: 3.1 – 73.5%), followed by general wards (21.9%, Q_{1-3}: 3.4 – 46.0%) and gynaecologic/obstetric wards (13.3%, Q_{1-3}: 0.0 – 45.6%, **Figure 2**).
- In the descriptive analysis, **only in women undergoing gynaecological/obstetric surgery the "institutional" percentage of opioid administration was associated with PROs** (**Figure 3**).
- **In the cluster analysis we identified 3 highly stable clusters of opioid administration** (**Figure 4**), which can be interpreted in terms of a **"liberal", "moderate" and "restrictive" opioid policy**.
- In the subsequent regression analyses we found **no clinical relevant differences in the PROs between the clusters** (**Figure 5**).
- **In the secondary cluster analysis considering the administration of specific opioids on the ward, we identified 6 clusters** (**Figure 6-A**). In the subsequent regression analyses we found **no differences in worst pain intensities** between the clusters (**Figure 6-B**). **Differences in pain interference and side effects were small to medium**.

CONCLUSION

In this study, we found that policies for administering opioids after surgery on the ward fell into three clusters: **liberal, moderate or restrictive policy**. We found **no clinically relevant differences in PROs** between clusters in either the primary analysis for mixed surgical procedures or the sensitivity analysis for specific surgical procedures. Differences in PROs were also small in the complex cluster analysis considering specific opioids. The results of this analyses point in the direction of **limited efficacy of opioids in the acute postoperative setting**. However, considering the limitation of registry-based studies, the results have to be interpreted with caution.

QUIPS

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